DO NOT CIRCULATE

UNIVERSITY OF MICHIGAN
OCT 13 1954
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 2 1954

TABLE OF CONTENTS

The Role of the Host in the Chemotherapy of Tuberculosis P. D'ARCY HART, M.D., F.R.C.P. 767
The Danger of Accidental Carbon Monoxide Poisoning KEITH SIMPSON, M.D. 774
Three Cases of Collagen Disease Treated with Corticoids D. G. RICHARDS, M.D., M.R.C.P. 777
Results of a Planned Attack on Carcinoma of the Vulva STANLEY WAY, F.R.C.O.G. 780
Treatment of Gout with H.P.C. D. N. ROSS, M.D., F.R.F.P.S. 782
Carotid-Cavernous Fistula JOHN M. POTTER, M.B., F.R.C.S. 786
Measles Meningoencephalomyelitis W. F. TWINING MCMATH, M.D., M.R.C.P., D.P.H. 789
Antagonistic Effect of A.C.T.H. and Cortisone on the Anticoagulant Activity of Ethyl Biscoumacetate JYOTI B. CHATTERJEA, M.D., and LUCY SALOMON 790
A Case of Uveitis with Deafness P. K. ROBINSON, M.B., M.R.C.P. 792

MEDICAL MEMORANDA

Liver Abscess and Polyarteritis Nodosa. IAN C. GILLILAND, M.D., M.R.C.P., and GEOFFREY C. MANNING, M.B., B.Ch. ..794
Recovery from Sterility after Mumps Orchitis. BERNARD SANDLER, M.D., D.M.R., D.R.C.O.G. 795

BOOK REVIEWS 796

GENERAL ARTICLES AND NEWS

Third International Congress of Nutrition 804
Third International Congress of Internal Medicine 805
MEDICAL DEFENCE UNION 807
CANCER EDUCATION BY TELEPHONE 807
ST. MARY'S HOSPITAL MEDICAL SCHOOL 808
MEDICAL NEWS 819
BIRTHS, MARRIAGES, AND DEATHS 820

QUESTIONS AND COMMENTS

Whooping-cough Immunization—Abdominal Testes—Diagnosis of Non-paralytic Poliomyelitis—Transplantation of Teeth—Blood Pressure and Pulse Rate—Tuberculosis from Pets—Alpha-naphthylamine and Cancer—Nerve Impulses and Tumour Growth—Adrenaline Test—Reliability of Mass Miniature Radiography—Itching in Hodgkin's Disease 821-2

LEADING ARTICLES

Disseminated Lupus Erythematosus 798
Doctors' Surgeries 799

ANNOTATIONS

Meigs's Syndrome 800
Treatment of Measles Encephalitis 801
Accidental Carbon Monoxide Poisoning 801
Dial C for Cancer 802
Is Mongolism a Metabolic Error? 802
100 Years of a Medical School 803

CORRESPONDENCE

Smoking and Cancer. R. DOLL, M.D., M.R.C.P., and A. BRADFORD HILL, D.SC., F.R.S. 808
Operative Cholangiography. R. J. MCNEILL LOVE, M.S., F.R.C.S.; M. J. SMYTH, F.R.C.S. 809
Galactosaemia. G. KOMROWER, M.B., and A. HOLZEL, M.D.; A. CASTELLANI, M.D. 810

SUPPLEMENT

Full Contents on First Page of Supplement

Surgery Premises 131
Hospital Administration 133
Correspondence:
Drugs for Private Patients. B. S. GRANT, M.B.; F. D. P. H. WARD, F.P.S. 134

CORRESPONDENCE—*cont.*

Visit to Poland. WINIFRED M. COPPARD, M.R.C.S. 810
Infant-feeding. A. GEORGE, M.B. 811
Drainage in Radical Mastectomy. C. C. K. SMITH, F.R.C.S. 811
Urology at St. John's, Lewisham. H. P. WINSBURY-WHITE, F.R.C.S. 811
C.S.F. Sugar in Tuberculous Meningitis. G. D. W. MCKENDRICK, M.R.C.P. 811
Incoagulability of Blood after Haemorrhage. W. N. ROLLASON, M.B., F.F.A. R.C.S., and A. J. SHILLITOE, M.R.C.P. 811
Pilonidal Sinus. D. WYNN-WILLIAMS, F.R.C.S. 812
The Dormant Cancer Cell. W. SAMPSON HANDLEY, F.R.C.S.; A. C. MORSON, F.R.C.S.; R. L. WORRALL, M.B. 812
Lung Cancer. A. G. MARSHALL, M.D.; G. R. OSBORN, M.B. 813

OBITUARY

R. Barclay Ness, M.B., C.M., F.R.F.P.S. ..814
J. C. Jefferson, M.B., F.R.C.S. 814
William Paterson, M.B. 815
C. L. Batteson, M.R.C.S., L.R.C.P. 816
L. R. Janes, M.A., M.B. 816
Marjorie Back, M.D., D.P.H. 817

Vital Statistics 817

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4891, WEEKLY, PRICE 3/-

Copyright

REGISTERED AS A NEWSPAPER

OCTOBER

THE BLIND SPOT

We live, it is frequently alleged, and learn. But some lessons are oddly elusive, and if, on the evening which sees the end of Summer Time, it were possible by some form of telepathic radar to conduct a nation-wide public opinion poll, there would be a striking lack of unanimity in our answers to the question: "Should the hands of the clock be put on or put back at the end of Summer Time?" One trusts that the putters-back would outnumber the putters-on; but it might not be by a very wide margin, and there would, one cannot help fearing, be a discreditably large total of "Don't Knows". Why, in almost every household, should summer's lease expire in a minor flurry of controversy? ("*But if we* gain *an hour, surely it doesn't make sense to put the clock* back." "*I'm positive that's what we did last year, dear. Don't you remember? I went and asked Mother . . .*") Why, every autumn, do we make such heavy weather of our elementary experiment with time?

None can say. We are a modest race. As our orators and our leader-writers frequently remind us, we are not given to bragging about those qualities of commonsense and good judgment to which, happily combined as they are with a lively imagination and a practical grasp of detail, we owe as a nation our reputation for sagacity. Our modesty is particularly appropriate at the end of Summer Time.

The change from Summer Time is the only occasion on which the Midland Bank 'puts back the clock'. In all other respects, its outlook is forward and its services as modern as today.

MIDLAND BANK

CASSELL MEDICAL BOOKS

CLINICAL PSYCHIATRY

by W. MAYER-GROSS, M.D., F.R.C.P.
ELIOT SLATER, M.A., M.D., F.R.C.P., D.P.M.
MARTIN ROTH, M.D., M.R.C.P., D.P.M.

The authors of this important new comprehensive textbook have approached their task in the belief that the foundations of psychiatry are laid in the ground of the natural sciences, especially neurophysiology and cerebral pathology. Their standpoint derives from the classical, and has led to an attempt to handle psychiatry along the lines of an essentially medical tradition. The discussions of the various forms of mental disorder are accordingly drawn up under the headings (such as may be found in any standard work on medicine): definition and classification, incidence, aetiology and pathology, clinical features, diagnosis, prognosis, and treatment.

672 pp., crown 4to, with 16 halftone plates. 50/- *net*

37/38 St. Andrew's Hill, London, E.C.

FIVE OUTSTANDING BOOKS

TEXTBOOK OF
OPERATIVE SURGERY
By
ERIC L. FARQUHARSON, M.D., F.R.C.S.
863 pages — 945 illustrations (many in colour) — 75s.

TUMOURS OF
LYMPHOID TISSUE
By
GEORGE LUMB, M.D.
212 pages — 205 illustrations — 37s. 6d.

SURGERY OF THE
CAECUM AND COLON
By
STANLEY AYLETT, M.B.E., M.B., B.Sc., F.R.C.S.
304 pages — 170 illustrations (20 in colour) — 45s.

PHYSICAL METHODS OF
TREATMENT IN PSYCHIATRY
By
WILLIAM SARGANT, M.B., F.R.C.P., and ELIOT SLATER, M.D., F.R.C.P
Third Edition — 371 pages — 20s.

THE PRINCIPLES AND PRACTICE OF
MEDICINE
A Textbook for Students and Doctors
Edited by
L. S. P. DAVIDSON, M.D., F.R.C.P.Ed., F.R.C.P.Lond.
Second Edition — 1048 pages — 101 illustrations — 32s. 6d.

Published by
E. & S. LIVINGSTONE, LIMITED
TEVIOT PLACE, EDINBURGH
Whose complete catalogue will be sent on request

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 2 1954

THE ROLE OF THE HOST IN THE CHEMOTHERAPY OF TUBERCULOSIS*

BY

P. D'ARCY HART, M.D., F.R.C.P.

From the Medical Research Council's Tuberculosis Research Unit and the National Institute for Medical Research, London

In the chemotherapy of tuberculosis, as of many acute infections, it is usual to consider principally the drug–parasite relationship. This concept has been very valuable, but it is becoming increasingly recognized that it takes insufficient account of the host. In a chronic infection like tuberculosis, host resistance may even influence the value of agents with direct and specific antibacterial action, while after discontinuation of chemotherapy many important tasks remain for the body's defences to tackle, aided, of course, by other forms of treatment. Furthermore, certain antituberculous drugs produce their beneficial effect through the host's defence mechanisms and not by directly damaging the bacillus. I propose, therefore, to discuss some aspects of the complicated relationship between the host, the tubercle bacillus, and the drug. I shall not attempt a general review of the factors believed to influence native and acquired resistance to tuberculosis, or of the varied mechanisms whereby the body's defences may destroy, or prevent, or in varying degrees even permit, bacillary multiplication ; this has been done excellently by others.

First, it is necessary to mention briefly some obvious host factors that may limit the efficacy of the drugs within the diseased tissues.

Physiological and Biochemical Factors

The maintenance of an effective concentration of a drug in a lesion will be determined by the levels attained in the blood ; the structure and vascularity of lesions, and other factors affecting the ease of dissemination to the site of infection (Florey, 1952) ; the ability to penetrate cells, especially monocytes (macrophages)—isoniazid penetrating well, streptomycin poorly, and *p*-aminosalicylate (P.A.S.) hardly at all (Mackaness, 1952 ; Mackaness and Smith, 1952) ; the destruction or alteration within the body—for example, by binding with proteins ; the susceptibility to antagonism by normal or pathological tissue constituents (Dubos, 1953a) ; the effect of the *p*H in the tissue environment ; and, finally, the rate of excretion.

Toxicity

Toxicity also may restrict the efficacy of the agent by setting an upper limit to dosage. There are sometimes marked species differences. Thus the dog is much more susceptible to isoniazid toxicity than man, and the monkey less (Schmidt *et al.*, 1953). As another striking example, a few years ago certain benzphenoxazines were reported to be more active than streptomycin against tuberculosis in mice, but, whereas toxicity for this species was found to be gratifyingly low, larger animals developed a haemolytic anaemia and humans could not tolerate even 1/100 of the mouse dose, body weight for body weight. Apart from such species differences, tests on animals may fail to show minor symptoms (for example, the gastro-intestinal disturbances associated with P.A.S.), or rare but more serious toxic manifestations (for example, drug allergic sensitivity to streptomycin and/or P.A.S.). It may be concluded that, whereas experimental animals may be a good guide to the clinical value of antibacterial agents, this is sometimes not the case for toxicity, and the first use in man himself must always be approached with the greatest caution.

*A lecture delivered in the series "The Scientific Basis of Medicine" of the British Postgraduate Medical Federation (University of London), in February, 1954.

THE INTERPLAY OF HOST RESISTANCE AND SPECIFIC ANTIBACTERIAL CHEMOTHERAPY

The natural history of an infectious disease largely reflects the native and acquired immunological resistance of the host. If the disease is chronic the prolonged course will give greater time for the defence forces to be deployed. If, in addition, a drug having a direct and specific effect upon the invading bacteria is administered, there will be some interplay between the host resistance and the antibacterial action of this chemotherapy. I shall suggest that there are two important phases in this interplay—an initial phase when the host may influence the destruction of the bacilli by the drug, followed by a phase, after discontinuation of the chemotherapy, when the ability of the body's defences to clear up residual infection, and of its repair processes to heal the lesions, may determine the outcome. Ultimately there may remain irremediable damage: destroyed lung, established bronchiectasis, cardiac complications, etc.

I shall consider in turn the phase of chemotherapy, and the subsequent phase after discontinuation. For simplicity a single course, without retreatment, is referred to. By combined therapy I mean treatment with more than one drug simultaneously.

(i) During the Chemotherapy

Early Improvement

Experiment and experience of human tuberculosis show that acute recent disease is, to begin with, particularly responsive to chemotherapy. Such acute forms of the disease indicate a relative failure of the host, due either to a low resistance or to an overwhelming dose of bacilli. From this it may be inferred that in some instances a low host resistance may actually favour chemotherapy, though this does not necessarily imply a greater overall benefit to the host.

Let me give some examples. In the highly susceptible guinea-pig, chemotherapy is more effective in acute tuberculosis than in the chronic disease (Steenken, Wolinsky, *et al.*, 1952). In more resistant man, too, acute recent exudative and acute miliary tuberculosis respond more quickly than do chronic forms (Medical Research Council, 1952b, 1953a; Bernard *et al.*, 1953; Zeichner and Childress, 1953). Patients under 40 tend to respond better than those older (Tucker, 1953), possibly because many of the latter have long-standing lesions. In the trial of streptomycin (without other drugs) in acute, progressive, recent pulmonary tuberculosis in young adults (Medical Research Council, 1948), the less ill patients showed greater radiographic improvement on streptomycin combined with bed rest than did the more acutely ill, presumably because of a higher host resistance in the former. Yet a comparison of the early progress of the streptomycin group with that of a control group treated by bed rest alone, so as to isolate the part played by the chemotherapy itself, showed that there was a better *response to chemotherapy* in the more acutely ill than in the less ill—that is, the contrast between the progress of the streptomycin and the control groups was greater for the more acutely ill than for the less ill patients. Similar results in acute and less acute cases were obtained in a U.S. Public Health Service trial (Long and Ferebee, 1950). It is also common clinical experience that in the chemotherapy of patients with chronic disease and recent spread, the recent spread shows the greater response. In a trial proceeding under Professor A. W. Williams and Dr. P. W. Hutton at Mulago Hospital, Uganda, in association with the Tuberculosis Research Unit, preliminary study of African patients with radiographically hyperacute pulmonary tuberculosis suggests that on similar regimes (streptomycin plus isoniazid, or P.A.S. plus isoniazid) their response over a three-months period was at least as great as the response of acute disease in Europeans.

If all this appears obvious now, it shows how our approach has changed. Ten or more years ago the selection of cases of acute pulmonary or miliary tuberculosis for clinical trial of a promising drug would have brought the protest that this was not giving the drug "a fair chance."

In the view of some, the greater responsiveness to chemotherapy of acute than of chronic, and even of hyperacute than of acute, lesions is related not so much to reduced host resistance as to anatomical differences—for example, in vascularity affecting arrival of the drug, and in elasticity and fibrosis affecting ease of healing (Carvalho, 1954). High fever itself has been proposed as promoting responsiveness to antibacterial agents, by enhancing their bactericidal action (Marks, 1951; Knox *et al.*, 1952). These considerations may well also be of importance, and in laying stress on host resistance I recognize that I am attempting to isolate a single factor out of many. Yet the very difficulty of clinical elucidation justifies a closer examination of a thesis that receives some support from recent laboratory studies.

Host Resistance and Drug Action

I should like here to discuss the experimental basis for believing that host resistance may influence response to drugs in tuberculosis.

There are three main issues: (1) Are the drug regimes currently used mainly bacteriostatic or bactericidal? (2) How far is their effect due to ability to penetrate into lesions and into macrophages within lesions? (3) What is the relative importance of the intracellular and extracellular battlefields during chemotherapy? It is still often assumed that the action of streptomycin, isoniazid, and P.A.S. *in vivo* is bacteriostatic rather than bactericidal (see d'Esopo, 1954). Moreover, certain types or parts of lesions are thought by some to be relatively inaccessible—for example, cavity walls; and drugs clearly vary much in their ability to penetrate into certain cells, such as macrophages (Barski, 1948; Magoffin and Spink, 1951; Mackaness and Smith, 1952, 1953; Suter, 1952). Thus the idea has grown that while chemotherapy inhibits the multiplication of tubercle bacilli they may survive and continue to multiply in certain protected sites. But a different view may well be taken. There is evidence that in full dosage isoniazid, and probably streptomycin, achieve bactericidal concentrations in many, if not all, types of lesion, particularly when given in combination (Steenken, d'Esopo, and Wolinsky, 1947; Smith and Waksman, 1947; Garrod, 1948, 1950; Barclay *et al.*, 1953; Canetti and Grumbach, 1953; Weiser *et al.*, 1953; Singh and Mitchison, 1954).

As regards penetration into cells, isoniazid, alone or with streptomycin, appears able to reach bactericidal concentrations even in macrophages (Mackaness and Smith, 1952, 1953). There is evidence, too, that with efficient antibacterial chemotherapy intracellular multiplication *in vivo* is less important in allergic animals and man than might be expected. (*a*) Since isoniazid enters macrophages well, streptomycin poorly, and P.A.S. hardly at all, the combinations P.A.S. plus isoniazid, and P.A.S. plus streptomycin, would be less effective than streptomycin plus isoniazid in preventing drug resistance, if intracellular multiplication were important: in actual fact, the efficacy of the three combinations in human pulmonary tuberculosis is of the same order (Medical Research Council, 1950, 1953a, 1953b, 1953c). (*b*) In pre-allergic guinea-pigs, lesions continue to enlarge and bacilli to proliferate intracellularly in spite of streptomycin treatment (Jensen, 1949; Steenken and Pratt, 1949), whereas in allergic (but susceptible) animals where the bacilli are more extracellular—for example, in guinea-pigs or in rabbits infected with bovine-type bacilli—the disease can be suppressed for long periods by continued treatment with streptomycin alone. (*c*) When macrophages die the intracellular bacilli will be liberated and therefore accessible to extracellular drug action, unless or until rephagocytosed. So the concept has developed that during efficient chemotherapy, such as with the usual combinations in full dosage (Medical Research Council, 1953a, 1953b), multiplication of bacilli is largely suppressed, and bactericidal action is the dominant event (Mitchison, 1954).

Let us consider the implications of this concept. Many workers have shown that for a rapid bactericidal effect by streptomycin or isoniazid *in vitro* a culture medium favourable to cell division is required, since the proportion killed in a medium that does not readily support growth is small or nil (Middlebrook and Yegian, 1946; Garrod, 1948; Szybalski and Bryson, 1953; Mackaness and Smith, 1953; Schaefer, 1954). If these findings hold good *in vivo*, then tubercle bacilli dividing slowly or not at all—for example, in quiescent or "closed" necrotic foci—will not be killed rapidly even by contact with bactericidal concentrations of drugs, while those accessible bacilli that have been multiplying rapidly will be particularly susceptible. Rapid growth will be favoured by weak or ineffective host defences; and, similarly, so will rapid killing of the bacilli by drugs.

It could thus be argued that it would be advantageous for a tuberculous patient to have a low resistance and a rapid division of the bacteria accessible to the drugs. Such might indeed be the case if specific drugs were so powerfully bactericidal as to overshadow the normal host defence mechanisms, resembling the successful chemotherapy of certain acute pyogenic infections that have not yet produced much pus or necrosis; for here the host's defences, at least its phagocytic activity, may play a minor part in overcoming the infection (Kaplan *et al.*, 1952; Gowans, 1953a; Bowden, 1953). This approximation to the test-tube may not yet be true of tuberculosis, even during prolonged combined therapy. The position here may be more comparable to acute infections treated with small doses of penicillin, where it can be shown that the host assists in disposal of the bacteria (Jawetz, 1946; Eagle *et al.*, 1950; Gowans, 1953b); or, better, to acute infections in the presence of pus and necrotic tissue (Florey, 1952). But in tuberculosis both the growth of the bacilli and the mobilization of the defence forces are much slower than in acute pyogenic infections.

Although it may be unwise to draw a close analogy between a tuberculous host on chemotherapy and an infected

culture containing a bactericidal agent, there remains, nevertheless, the possibility that organisms dividing slowly in the body or "resting"—for example, in necrotic foci—are an obstacle to effective tuberculocidal therapy. Short of drugs able to kill resting bacilli within tissue cells, a stimulus both to multiplication of such refractory organisms and to their liberation into the extracellular drug pool might assist. The stimulus might come from an agent that lowers host resistance—for example, cortisone, which has been reported to improve the therapeutic response when given with large doses of isoniazid to tuberculous mice (Ilavsky and Foley, 1953). Apart from the risk of stimulating such growth, any improved chemotherapeutic action in human tuberculosis would have to be weighed against the possible danger of reducing the help given by normal host defences in overcoming the infection. In this connexion, it would be interesting to know whether suitably selected patients with non-acute lesions would do better than a comparable group treated in bed if the host's defences were lowered by keeping the patients ambulant during a course of chemotherapy.

Meantime, further knowledge of the early reaction to chemotherapy of comparable forms of tuberculosis in persons with presumably low and high host resistance is desirable—for example, in the malnourished as compared with the well-nourished, diabetics with non-diabetics, as well as in the presumed "susceptible" ethnic groups in which the disease is expected to run a more rapid course than in others (Daniels *et al.*, 1948). With increasingly powerful chemotherapy does the apparently disadvantageous factor of low resistance matter less? Or may it be a positive advantage? And if this is the case initially, what is the position after discontinuation of chemotherapy? Does a lower native resistance, often combined with a bad environment, assert itself by a tendency to later reactivation—a vital therapeutic problem in underdeveloped communities? And, granted that the patient already possesses some degree of allergy, what effect might tuberculin desensitization, which it is claimed can be produced in man by large oral doses of B.C.G. (see Fourestier and Blacque-Belair, 1954), have upon his response to chemotherapy? Answers to some of these questions might be aided by experimental work on the chemotherapeutic response in animal families inbred so as to be either highly susceptible or highly resistant to tuberculosis (Lurie, 1950; Lurie *et al.*, 1953b), and in susceptible animals whose resistance has been increased by B.C.G. immunization (Jensen, 1949).

Drug Resistance

Having discussed the effect of the host on the antibacterial activity of drugs, I shall now turn to an aspect of the initial phases of chemotherapy which concerns more particularly the parasite–drug relationship—namely, drug resistance. This plays an important part in the response to treatment, especially by a single drug. If, as is usual, it is assumed that resistant strains emerge owing to the selection of resistant mutants, then the appearance of such strains in a patient treated with a single drug will depend upon the number of such mutants present before treatment, the degree of their drug resistance, and their rate of growth. The larger the initial bacterial population, the greater will be the number of resistant mutants present before treatment. The rate at which they grow may be determined not only by the dosage of the drug given but by the state of the host's defences.

Thus, as is well known, after some weeks' treatment of acute pulmonary tuberculosis with either streptomycin, isoniazid, or even P.A.S., used alone, drug-resistant strains of bacilli are frequently found in the sputum (Medical Research Council, 1948, 1950, 1952b), and eventually may largely replace a declining population of sensitive organisms (Crofton and Mitchison, 1948; Mitchison, 1950; Joiner *et al.*, 1952). This emergence is particularly rapid and intense in patients with large cavities and, in the case of streptomycin at least, with severe constitutional disturbance, when treatment is started—that is, in those patients who probably have a large initial bacterial population and weak host defences (Medical Research Council, 1948, 1950, 1954b). The drug-resistant bacteria may be so numerous that in the dosage given the drug is no longer effective. This has been clearly demonstrated in treatment with streptomycin (Daniels and Hill, 1952). Failing the use of another drug, the subsequent course of the disease will be determined by other general measures, by collapse therapy or resection, and by the host's defences. The part played by the last is discussed later.

Combined chemotherapy has a decisive effect on drug resistance, provided the bacilli before treatment are sensitive to both drugs. If the drugs and doses are correctly chosen, not only may there be an additive or synergistic antibacterial effect, but drug resistance is largely prevented. In the Medical Research Council trials of streptomycin plus P.A.S., streptomycin plus isoniazid, and P.A.S. plus isoniazid, only 1–5% of patients with initially sensitive strains yielded cultures resistant to either drug after treatment for three months (Medical Research Council, 1950, 1953a, 1953b, 1953c), while in some 70% of patients the sputum was bacteriologically "negative." Information is not clear on how far the tendency—noted in certain single-drug treatments—for drug resistance to be commoner in patients likely to have a large initial bacterial population and poor defence mechanisms holds under combined therapy; the small numbers of resistant strains make analysis difficult (Medical Research Council, 1950, 1952a). The possibility that drug resistance during combined therapy can be transitory is discussed by Mitchison (1954).

(ii) After Discontinuation of the Chemotherapy

After the chemotherapy has been discontinued the role of the host's defences is more straightforward. In the, as yet unlikely, event of complete eradication of the infecting bacteria from the lesions, the danger of relapse would be removed, though resulting damage might persist. If, however, chemotherapy can do no more than help in stabilizing lesions, in closing cavities, and in reducing the volume of infection, the body's defences, together with other medical and surgical measures, may subsequently complete the healing process. A small residual infection may indeed act as a continued immunizing agent, but such possible advantage must be weighed against the risks due to the presence of virulent bacteria.

Relapse in Experimental Tuberculosis

Sterilization of the lesions by chemotherapy is still an uncommon finding in experimental tuberculosis, provided bacteriological examinations are complete (Jensen, 1949; Dubos, 1953a; Hobby *et al.*, 1953; Karlson and Feldman, 1953; Siebenmann, 1953). Nevertheless, recent combinations of drugs may have nearly achieved this object.* Where treatment has not resulted in sterilization, the incidence of relapse after withdrawal has varied with the animal species, as well of course as with the drug. In the guinea-pig, primary infection with a few virulent bacilli is fatal (Wilson and Miles, 1946), and experimental chemotherapy has so far usually left so large a bacterial population, and also so much tissue damage, that the native and acquired host resistance and the repair processes have been unable to cope. Reactivation with slowly progressive chronic but fatal disease usually results after withdrawal of the drugs, similar to that observed in the guinea-pig vaccinated with B.C.G. and subsequently given a small virulent infection (Schwabacher and Wilson, 1938; Steenken and Wolinsky, 1947, 1952; Jensen, 1949; Steenken, Wolinsky, *et al.*, 1951, 1952).

In the more resistant mouse, primary infection with moderate intravenous doses of tubercle bacilli kills with acute disease, but sufficiently small doses by this route have, in our hands, produced a chronic, relatively non-progressive, though damaging, disease, and this host–parasite equilibrium has been maintained for many months (Hart and Rees, 1950).

*See McDermott *et al.* (1954) on pyrazinamide-isoniazid combination.

Fatal reactivation, however, occurs if resistance is lowered by cortisone. Although in mice, too, relapse has usually followed sooner or later after withdrawal of chemotherapy (Martin and Stewart, 1950; J. Hirsch, 1953), recently this has not happened after cessation of streptomycin plus isoniazid in the treatment of intracorneal infection of mice (Goulding and Robson, 1952). It may well be that this powerful combination can reduce the bacterial population to a level corresponding to that productive of a non-fatal equilibrium. In the rabbit, whose resistance to human-type bacilli is still higher than that of the mouse, it is even more probable that relapse after chemotherapy could be prevented. On the whole, then, the evidence suggests that with increasingly efficient combinations the tendency to relapse may be reduced or abolished, especially in species with relatively high native resistance.

Relapse in Clinical Tuberculosis

In man the part played by the host defences in subsequent progress and in prevention of relapse after discontinuation of chemotherapy is difficult to disentangle from the part played by further medical and surgical measures, and by any further chemotherapy. Some valuable information is now available from a five-year follow-up of the original streptomycin trial patients mentioned earlier (Medical Research Council, 1948), undertaken in the Tuberculosis Research Unit (Fox *et al.*, 1954). These patients were a fairly homogeneous group of young adults with recent acute extensive bilateral pulmonary tuberculosis. Fifty-five patients had been given bed rest and streptomycin (alone), 2 g. daily, for four months; 52 control patients with comparable disease had received bed rest alone. Over a period of six months the streptomycin patients had fared much the better, as regards both mortality and radiographic change. Incidentally, this generally good initial response in a grave form of tuberculosis showed in 1947–8 what a powerful new weapon had arrived.

Few patients in either group received further chemotherapy, but more of each group received collapse therapy, and allowance for this must be made in interpreting the long-term results. Analysis of the survival figures up to five years from entry shows a gradual deterioration of the position in both groups. Each group, however, shows evidence of host resistance (fortified to some extent by collapse measures), for a proportion have survived and in some of these the disease is arrested, the experience of the streptomycin group being rather better than that of the controls. The follow-up period has been long enough to make the host's resistance the dominant influence at five years. The emergence of drug-resistant bacteria in most of the streptomycin group will account for its limited effect, the period of effective treatment being shortened; consequently the bacterial content of the sputum generally rose during the latter part of the chemotherapy, tending to present the body's defences once again with a bacterial population approaching that at the start of treatment (Medical Research Council, 1948). Another factor to be considered is the virulence of streptomycin-resistant organisms; there is, however, no conclusive evidence on whether these are more or less virulent than sensitive ones (Youmans and Williston, 1946; Steenken and Wolinsky, 1948; Emmart *et al.*, 1949; Feldman *et al.*, 1948; Rosa *et al.*, 1953); if anything they may be somewhat less virulent.

In order to obtain a closer view of the course of the disease in these two groups over the five years, Fox *et al.* have related mortality from four months onwards to the response during the first four months (as shown by *x*-ray changes and other clinical criteria). This analysis suggests that patients with a high host resistance or less extensive disease tended to survive even without the assistance of streptomycin. In contrast are those with very extensive disease or low host resistance, and a bad immediate prognosis if treated by bed rest alone; for although such patients improved while the bed rest was supplemented with streptomycin, their defences were unable to maintain this advantage and they tended to die later.

It may be concluded that a period on streptomycin assisted some patients with more effective host defences, but did little more than delay the subsequent mortality of most of those with poor or ineffective defence mechanisms. For the host's defences and repair processes to deal satisfactorily—on a long-term basis—with disease of this nature and extent, even with the help of collapse measures, more is clearly needed than bed rest plus therapy with a single drug, at least with streptomycin.

Although the limitations of streptomycin were soon recognized, the follow-up of the ultimate fate of patients treated with it in comparison with an untreated control group is valuable: hence the stress I have laid on this study even though the regime is outdated. We may hope that the long-term follow-up of patients with the same type of acute disease in the Medical Research Council trials, but treated with combinations of antibacterial drugs, will show a very different picture.

Bacteriological data are not available for the later periods of the long-term streptomycin follow-up referred to, but they should be attempted in future inquiries. It would be useful to know, first, what proportion of patients relapse bacteriologically, and, secondly, whether a positive sputum from a patient in relapse contains resistant or sensitive organisms. A negative sputum does not, of course, mean certain absence of organisms from the tissues. When sensitive organisms persist after withdrawal of chemotherapy, it may be because they are in sites containing bacilli either in a resting state or slowly dividing, and have therefore escaped the bactericidal action, as suggested earlier (see also Bigger, 1944; Jensen, 1949; Mitchison, 1954). Thus in closed necrotic lesions the body's defences may discourage bacterial survival or growth; such lesions may even be increased by the chemotherapy, but if resistance is lowered, bacilli surviving in them may multiply and appear in the sputum (see Canetti, 1946; Jensen, 1949; Medlar, 1952; Yegian, 1952; Pagel, 1952; Dubos, 1952, 1953a; d'Esopo, 1954). Sensitive organisms may persist in lesions also because the drugs have failed to reach the bacilli in phagocytic cells (Mackaness and Smith, 1952, 1953) or have been antagonized by substances in the lesions (Dubos, 1953a).

Like persistent sensitive organisms, residual resistant bacilli can be a cause of relapse, and there is the added risk that they will become numerous enough to contain mutants resistant to other drugs as well, thus complicating retreatment (Mitchison, 1954).

Some of these points are illustrated by a year's observation of sputum changes in the Medical Research Council isoniazid trial (unpublished data). The patients had various types of pulmonary tuberculosis and had been treated with streptomycin plus isoniazid, or streptomycin plus P.A.S., for three months (no further chemotherapy had been given, but some patients had had collapse therapy). The majority who had negative sputa at the end of the three-months course still had negative sputa nine months later. In a small proportion the sputum had become positive again, though the bacilli were still sensitive; on the other hand, in some of the patients yielding sensitive organisms after three months' treatment the sputum was negative nine months later. There were too few cases with resistant strains after combined therapy for conclusions to be drawn at the end of the year, but we may compare this position with the not inconsiderable incidence of resistant strains present after three months of isoniazid alone and still present nine months later (Medical Research Council, 1954a). Combined therapy, then, produces a fairly satisfactory bacteriological result, but the host's defences also contribute by restraining relapse and reducing residual infection.

To summarize, interplay between host resistance and antibacterial chemotherapy is evidently complex. *During chemotherapy* we may conceive that a temporarily lowered host resistance may in certain circumstances lead to increased bactericidal effectiveness; but it may also favour the emergence of drug-resistant organisms. The effect of these two opposing tendencies will be influenced by the power and

the type of the chemotherapy. The picture is complicated by the usual struggle between the host's defences and the infection. *After withdrawal of chemotherapy* the role of the host defences in tackling residual infection is obviously more straightforward and akin to the usual host–parasite relationship: further medical and surgical interventions may also have to be taken into account.

I now turn to a further part of the subject, in which the host and its defences against the infection are more essentially involved in the drug's action.

HOST SIDE-EFFECTS OF POSSIBLE RELEVANCE

Apart from their direct antibacterial action, some antituberculous agents have other effects which could influence the therapeutic result. Thus the thiosemicarbazones may reduce allergy and tuberculin sensitivity, and may also have a thiouracil-like effect on the thyroid gland (see Staub, 1953). P.A.S. has antipyretic and other salicylate actions and also an antithyroid action (Hamilton, 1953; Beattie and Chambers, 1953); it is reported to be antihistaminic and anti-inflammatory (Forró and Szegö, 1951). Alterations in vascularity of lesions after isoniazid treatment have been described (Panà *et al.*, 1952; Dick, 1953). According to several authors, P.A.S., streptomycin, and thiacetazone ("conteben") accelerate mobility and phagocytic activity of leucocytes (Ozeki, 1952, 1953), and, it is claimed (Mauer, 1952a, 1952b), affect carbohydrate and intermediate phosphate metabolism, so leading to decreased tissue necrosis.

CHEMICAL AGENTS APPARENTLY ACTING ESSENTIALLY THROUGH THE HOST'S DEFENCE MECHANISMS

A small but interesting group of substances probably influence tuberculous infection through the host, and without direct antibacterial action. Not so long ago most remedies in tuberculosis were, in fact, directed primarily to affecting the host—for example, rest, sunlight, good food, traditional remedies such as cod-liver oil and calcium preparations, and "sanocrysin" (sodium aurothiosulphate) and other metal compounds thought to stimulate the tissues (see Hart, 1946). Thus it was quite reasonable for an authority on chemotherapy to conclude as recently as 1935 that "no treatment at present can be aimed directly against the causal agent . . . and the only procedures commonly approved consist in conserving general health, resting affected parts, and removing necrotic tissue"; though he added the belief that methods of directly attacking the tubercle bacillus would come (Browning, 1935). With successful specific drug treatment interest became focused on the straightforward interaction between drug and bacillus. But the chronic nature of tuberculosis, modified by fluctuating immunity and allergy, encourages the further search for artificial means of enhancing the operation of the host defences.

Lurie (1950), Florey (1952), and others have paved the way to a rational approach by analysing the normal defence mechanisms, with special emphasis on the functions of the monocytes (macrophages) and on penetrability of drugs into inflammatory areas. Discovery of an agent that decreases host resistance could be as valuable in the long run as of one that increases it, for even a "protuberculous" action demonstrates the flexibility of an element in the defence mechanisms, and might therefore give a lead to the discovery of an antituberculous agent involving the same element. Moreover, in certain infections alterations in dosage have been reported to change a protuberculous into an antituberculous effect—for example, cortisone in experimental pneumococcal infection (Robinson *et al.*, 1953).

First is the effect of dietary constituents. Yet in spite of the strong circumstantial evidence of the influence of nutrition upon susceptibility to human tuberculosis (Clarke, 1952; Helweg-Larsen, 1952), animal experiments have only recently begun to throw light on the nutrients involved (see Hart and Rees, 1950; Nègre, 1950; Bloch, 1953; Dubos and Pierce, 1954). Calciferol, it is true, gives undeniable clinical benefit in lupus vulgaris, possibly by enhancing some cellular reaction; but no such effect has been reported in systemic tuberculosis in laboratory animals.

With the exception of cortisone, the effect of hormones is uncertain. Large doses of chorionic gonadotrophin aggravate, and oestrogen suppresses, intracutaneous infection in highly inbred rabbits of genetically uniform stock, and the mechanism of this effect has been carefully analysed (Lurie *et al.*, 1949); but no effect has been shown with these two hormones in chronic mouse tuberculosis (Rees and Hart, unpublished), while large doses of oestrogen are said to accelerate infection in guinea-pigs (Svedberg, 1951). Cortisone, however, is the first hormone to be found capable of producing an unequivocally increased susceptibility to tuberculosis. In pharmacological doses in the mouse, it exacerbates a stable chronic infection and renders an acute infection hyperacute (Hart and Rees, 1950); and our findings have been confirmed not only in this species (Solotorovsky *et al.*, 1951; Engbaek *et al.*, 1952), but also in the rat (Michael *et al.*, 1950; Cummings *et al.*, 1952), to some extent in the rabbit (Ebert, 1952; Lurie *et al.*, 1953a; Morgan *et al.*, 1954), and even in man (American Trudeau Society, 1952).

The characteristics and mechanism of the phenomenon, mediated through the host but to a different degree in different species, are fully discussed by Rees (1954). Our attempts to exploit it have been unsuccessful, since no other structurally related steroid produced the effect in mice, except hydrocortisone (Kendall's compound F) and to a small degree Kendall's compound A (Rees and Hart, unpublished): the chemical specificity of the protuberculous action appears to coincide with that of the antirheumatic effect in man and of the depression of tuberculin sensitivity in the guinea-pig (Long and Spensley, 1954). Moreover, we have been unable to antagonize the protuberculous effect by any structurally similar steroid; and although Lemonde *et al.* (1952) have claimed to have done this with somatotrophic hormone (S.T.H.) in rats, and even to suppress experimental tuberculosis in mice with this hormone, we have failed to produce either effect in mice (Rees and Hart, unpublished). I have already mentioned the possibility of giving cortisone to stir up a stable chronic tuberculous infection, along with antibacterial therapy to deal with the bacilli multiplying and liberated from the cells (Ilavsky and Foley, 1953): the agents must be in maximum dosage, otherwise the use of cortisone might prove a disadvantage (Spain and Molomut, 1950; Bloch *et al.*, 1951; Cummings *et al.*, 1952; Meyer *et al.*, 1952; Jawetz and Merrill, 1953).

There are other instances where a change in the host–parasite relationship in favour of the tubercle bacillus has been brought about by a chemical substance. Quartz dust in the lung increases susceptibility to tuberculosis, as is well known. Even more striking is the observation that in silicotic guinea-pigs infected with B.C.G. the organisms were rendered pathogenic and the animals died with silicotuberculosis; but the virulence of the B.C.G. when recovered was unaltered (Vorwald *et al.*, 1950). Injection of beryllium chloride in guinea-pigs can also aggravate tuberculous infection (Weimer *et al.*, 1953). Procaine ("novocain"), pentobarbitone sodium, and the antipyretic phenamine (phenocoll hydrochloride) are said to worsen experimental tuberculosis, the suggestion being that neural conductivity is reduced and the influence of the central nervous system upon host resistance consequently disturbed (Kan, 1953). Mice rendered diabetic with alloxan showed no increased susceptibility to tuberculous infection (Hart and Rees, 1950), but rats, similarly treated, did (Roche *et al.*, 1952). None of these protuberculous effects has so far led to the discovery of a counter-agent.

Certain substances, without being themselves antibacterial, have been tested as auxiliaries to specific antituberculous compounds. Potassium iodide, ineffective by itself, but believed to promote digestion of caseous matter and so to liberate the bacilli and render them more accessible,

has been given simultaneously with streptomycin, with superior results to streptomycin alone in the tuberculous guinea-pig (Woody and Avery, 1948) and in tuberculosis of the rabbit's cornea (Rees and Robson, 1950). Phlorizin, stated to reduce tissue necrosis in tuberculous guinea-pigs by action on phosphate and carbohydrate metabolism, without direct effect on the bacteria, is claimed to act synergistically in combination with isoniazid (Mauer and Finkeldey, 1952, 1953). I do not know of any definite information on the clinical value of such auxiliaries.

Attempts have been made to improve the therapeutic effect by changing the level of tuberculous allergy in one or other direction. Tuberculin has been given intrathecally with streptomycin in tuberculous meningitis in order to promote an acute inflammatory reaction, resolve the exudate, and consequently to liberate bacilli to come into contact with the drug (Smith and Vollum, 1950; Smith, 1953). Before the risk was fully appreciated, cortisone and corticotrophin (A.C.T.H.), both of which depress tuberculin sensitivity in the guinea-pig (Long and Miles, 1950) and in man (Lovell *et al.*, 1953), were used clinically in the hope of reducing tuberculous hyperacute inflammatory phenomena (see American Trudeau Society, 1952, and LeMaestre *et al.*, 1953). More recently, however, A.C.T.H. has been used, with apparent safety, together with streptomycin and P.A.S., to desensitize patients with allergic drug reactions (Houghton, 1954).

On account of toxicity, or for technical reasons, none of the other substances shown to reduce tuberculin sensitivity in guinea-pigs (Fisher *et al.*, 1951; Long *et al.*, 1951; Cornforth and Long, 1952) has been tested in human tuberculosis. Nevertheless, on the view that tuberculin allergy has mainly a nuisance value, Brownlee (1953) has expressed the hope that specific drugs capable of blocking this reaction will be found useful clinically. In this connexion, it should be borne in mind that experimentally, and possibly clinically, tuberculin skin sensitivity can be substantially reduced or removed without loss of immunity (Wells and Wylie, 1952; and see Fourestier and Blacque-Belair, 1954), and that the bacillary constituents responsible for inducing allergy and immunity appear to differ (Raffel, 1950).

Surface-active Agents

Recently the first example of substances that exert a powerful suppressive effect on systemic experimental tuberculosis, apparently through the mediation of the host, was discovered at the National Institute for Medical Research (Cornforth *et al.*, 1951, 1954a, 1954b). Certain non-ionic surface-active polyoxyethylene ethers were found to be antituberculous when given parenterally to mice. Later, a curative effect was noted in established disease in guinea-pigs (Rees, 1953). Our original observation was made with commercial "triton A 20," but subsequently many agents with similar structure were synthesized. Two series have been principally studied, both having as starting-point *p-tert*-octyl phenol, which was condensed with formaldehyde. In the first series a complex resinous mixture of linear polynuclear products was thus formed. This intermediate mixture was reacted with ethylene oxide so as to give an optimal average length of polyoxyethylene chains, a soluble surface-active product resulting. In the second, more recent, series the formaldehyde condensation was carried out under different experimental conditions, and two pure crystalline intermediates were obtained having a macrocyclic tetranuclear structure and probably representing two of four possible geometrical isomers; these compounds were condensed similarly with ethylene oxide to form soluble surface-active products (mean molecular weight of those with an average of 20 ethylene oxide units per phenolic nucleus = about 4,000).

The biological properties of these products are summarized elsewhere (Rees, 1954). Owing to liver damage after continued administration in experimental animals, they have not been tried in man. In the present context the important findings are that they are not bacteriostatic *in vitro* and may even facilitate submerged and surface growth; while tubercle bacilli grown in them, or recovered from treated animals, show no decrease in virulence. Nor is there experimental evidence that *in vivo* (in mice) they counteract the toxic effect of the "cord factor," which is believed to contribute to the virulence of tubercle bacilli (Bloch, 1950, and unpublished). A point of special interest is that their antituberculous action is reduced and eventually abolished by lengthening the chains of the attached ethylene oxide units. The effectiveness of simultaneous administration of triton A 20 and dihydrostreptomycin in mouse tuberculosis has been reported by Solotorovsky and Gregory (1952).

That host defence mechanisms are essentially involved in the mode of action of these surface-active agents was first presumed by us on negative evidence—namely, lack of direct antibacterial effect *in vitro*, and failure to obtain evidence of conversion into antibacterial compounds in the body—for example, in the blood (Rees, 1953). Moreover, it seemed that the entire and fully developed host is required for the operation of these substances, since they failed to protect chicken embryos infected with tubercle bacilli when administered to the yolk sac, allantoic cavity, or intravenously (G. E. Davies, unpublished). Two relevant effects upon the host are, however, now known. One is a depression of tuberculin sensitivity in guinea-pigs, comparable in degree to that by cortisone but different in mechanism (Hart *et al.*, 1952). Interestingly, this anti-allergic effect was given only by therapeutically active members of the series tested; it is nevertheless uncertain how far it has any causal connexion with the antituberculous action.

The other host effect is upon the monocytes (macrophages), which was discovered recently at Oxford by Mackaness (1954a). Tubercle bacilli were introduced *in vitro* into preparations of monocytes obtained from animals previously injected with commercial "triton WR 1339" (the effective agent in triton A 20); although the rate of phagocytosis was not increased, the ingested bacilli were killed or their growth was inhibited, in contrast to the free intracellular multiplication seen under these conditions in monocytes isolated from untreated animals. Direct contact of the agent, in the limited concentrations tolerated by the surviving-cell preparations, with monocytes obtained from untreated animals was ineffective. It has since been shown (Lovelock and Rees, to be published) that the monocytes from similarly pre-treated animals contain the agent. These important observations suggest that one site, though not necessarily the only one, of the antituberculous action of these surface-active polyoxyethylene ethers in the body may be within the phagocytic host-cells of the infected tissues. How the agents enhance the operation of the cellular defences is not yet decided. They may bring about an alteration in the monocytes of treated animals, or they may affect the bacilli within the monocytes in some physical manner so as to make them more susceptible to the intracellular environment.

The production of an antituberculous effect by a chemical agent, probably operating through the host rather than by directly damaging the bacillus, opens out interesting prospects. First, it is possible that such agents, having no direct antibacterial action, might not induce drug resistance. Secondly, they might be used in combination with specific antibacterial agents. Thirdly, they might be used to strengthen host defence even after the withdrawal of chemotherapy. In the search for new agents, surface activity and macromolecular nature, and perhaps physical properties as much as chemical structure, might be used as a working guide. A practical difficulty is that assessment of activity of new compounds of this type is laborious, since they would be missed *in vitro*. For example, three leading American investigators (Youmans *et al.*, 1953) recently reported results of 3,500 organic compounds "screened" for antituberculous activity *in vitro*; the 184 active compounds discovered were then tested in mice. To test the remaining 3,316 substances primarily in mice in our own laboratory might have taken 25 years.

CONCLUSION

Consideration of host–parasite relations, complicated by a drug as a third party whose action may both influence and be influenced by them, suggests that we might regard some of the body's own defences as themselves acting like drugs. Such a view has some basis if it be accepted that interference with growth and survival of tubercle bacilli within macrophages is a feature of high native resistance and acquired immunity (Canetti, 1946; Lurie, 1950; Rich, 1951; Lurie *et al.*, 1952, 1953b; Suter, 1953). (The experiments of Brieger *et al.* (1951) and of Mackaness (1954b), however, throw some doubt on this action of monocytes.) In conformity with this concept, Dubos and Hirsch (Dubos, 1950, 1952, 1953b; Hirsch and Dubos, 1952; Hirsch, 1953, 1954) have suggested that certain substances with *in vitro* tuberculostatic or tuberculocidal properties may play a part in host defence by creating an unfavourable physico-chemical environment for the parasite. These include certain organic acids that may arise from metabolism of macrophages and from breakdown of tissue cells in inflammatory and caseous areas; lysozyme, which also occurs in inflammatory areas; and the polyamine spermine, and a peptide, both of which are found in some normal organs. The idea of "combined internal chemotherapy" cannot, of course, be applied to all aspects of defence. It is also one-sided, since the host tissues can also be looked on as a culture medium, some cells giving support and comfort to the enemy. But the idea may stimulate development of knowledge of the host–parasite–drug relationship in tuberculosis, more especially when considering drugs that might strengthen the host's own "chemotherapeutic" contribution to the struggle against the infection.

Ehrlich's famous conception of chemical compounds for which the disease-germ cells have a great affinity, while the body cells have little or none (Galdston, 1940; Hart, 1946), has been fulfilled for bacterial infections by penicillin, and to a less extent by other agents, including some of the anti-tuberculous drugs in current use. The surface-active agents described hold out hope of clinically useful compounds in whose action certain of the body tissues play an essential part, while the tubercle bacillus is not directly injured by the drug. If this turns out to be true it will be a modification of Ehrlich's original conception. Nevertheless, this way too may lead to his objective of chemical substances that will destroy the invading parasite without harm to the host; but the method of arriving there will be different.

In preparing this lecture I have drawn freely on the work and ideas of colleagues associated with the Medical Research Council's investigations in tuberculosis. I am particularly indebted to Dr. R. J. W. Rees, National Institute for Medical Research; Dr. Wallace Fox, Tuberculosis Research Unit; Dr. D. A. Mitchison, Postgraduate Medical School of London; and Dr. Ian Sutherland, Statistical Research Unit (Medical Research Council); as well as to the late Dr. Marc Daniels.

REFERENCES

American Trudeau Society (1952). *Amer. Rev. Tuberc.*, **66**, 254, 257.
Barclay, W. R., Ebert, R. H., Le Roy, G. V., Manthei, R. W., and Roth, L. J. (1953). *J. Amer. med. Ass.*, **151**, 1384.
Barski, G. (1948). *Ann. Inst. Pasteur*, **74**, 1.
Beattie, J., and Chambers, R. D. (1953). *J. Endocr.*, **10**, 65.
Bernard, E., Kreis, B., and Lotte, A. (1953). *Presse méd.*, **61**, 681.
Bigger, J. W. (1944). *Lancet*, **2**, 497.
Bloch, H. (1950). *J. exp. Med.*, **91**, 197.
—— (1953). *Ann. Rev. Microbiol.*, **7**, 19.
Bloch, R. G., Vennesland, K., and Gurney, C. (1951). *J. Lab. clin. Med.*, **38**, 133.
Bowden, J. (1953). *Brit. J. exp. Path.*, **34**, 497.
Brieger, E. M., Fell, H. B., and Smith, B. R. (1951). *J. Hyg., Camb.*, **49**, 189.
Browning, C. H. (1935). *Trans. roy. med.-chir. Soc., Glasg.*, **30**, 1.
Brownlee, G. (1953). *Pharmacol. Rev.*, **5**, 421.
Canetti, G. (1946). *Le Bacille de Koch dans la Lésion Tuberculeuse du Poumon*. Flammarion, Paris.
—— and Grumbach, F. (1953). *Ann. Inst. Pasteur*, **85**, 380.
Carvalho, L. de (1954). *Bull. Int. Un. Tuberc.*, **24**, 113.
Clarke, B. R. (1952). *Causes and Prevention of Tuberculosis*, p. 91. Livingstone, Edinburgh.
Cornforth, J. W., Hart, P. D'Arcy, Nicholls, G. A., and Rees, R. J. W. (1954a). *Proc. 6th Int. Congr. Microbiol.*, 1953. In press.
—— —— —— —— and Stock, J. A. (1954b). *Brit. J. Pharmacol.* In press.
—— —— Rees, R. J. W., and Stock, J. A. (1951). *Nature, Lond.*, **168**, 150.
—— and Long, D. A. (1952). *Lancet*, **1**, 950.
Crofton, J., and Mitchison, D. A. (1948). *British Medical Journal*, **2**, 1009.
Cummings, M. M., Hudgins, P. C., Whorton, M. C., and Sheldon, W. H. (1952). *Amer. Rev. Tuberc.*, **65**, 596.
Daniels, M., and Hill, A. B. (1952). *British Medical Journal*, **1**, 1162.
—— Ridehalgh, F., Springett, V. H., and Hall, I. M. (1948). *Tuberculosis in Young Adults* (Prophit Tuberculosis Survey, Roy. Coll. Phys.). Lewis, London.
Dick, J. C. (1953). *Lancet*, **1**, 808.
Dubos, R. J. (1950). *J. exp. Med.*, **92**, 319.
—— (1952). *Amer. Rev. Tuberc.*, **65**, 637.
—— (1953a). Ibid., **67**, 874.
—— (1953b). *J. exp. Med.*, **97**, 357.
—— and Pierce, C. (1954). *Tubercle*, **35**, September. In press.
Eagle, H., Fleischman, R., and Musselman, A. D. (1950). *Ann. intern. Med.*, **33**, 544.
Ebert, R. H. (1952). *Amer. Rev. Tuberc.*, **65**, 64.
Emmart, E. W., McClosky, W. T., Smith, M. I., and Lieberman, J. E. (1949). Ibid., **59**, 438.
Engbaek, H. C., Friis, Th., and Teilum, G. (1952). *Acta path. microbiol. scand.* **31**, 317.
d'Esopo, N. D. (1954). *J. Amer. med. Ass.*, **154**, 52.
Feldman, W. H., Karlson, A. G., and Hinshaw, H. C. (1948). *Amer. Rev. Tuberc.*, **57**, 162.
Fisher, N., Harington, C. R., and Long, D. A. (1951). *Lancet*, **2**, 522.
Florey, H. (1952). *Proc. roy. Soc. Med.*, **45**, 71.
Forró, L., and Szegö, L. (1951). *Acta physiol. Acad. Sci. hung.*, **2**, 415. Abstract in *Chem. Abstr.*, 1953, **47**, col. 5543.
Fourestier, M., and Blacque-Belair, A. (1954). *Les Anergies Cutanées Tuberculiniques*. Maloine, Paris.
Fox, W., Sutherland, I., and Daniels, M. (1954). *Quart. J. Med.*, **23**, 347.
Galdston, I. (1940). *Bull. Hist. Med.*, **8**, 806.
Garrod, L. P. (1948). *British Medical Journal*, **1**, 382.
—— (1950). *Amer. Rev. Tuberc.*, **62**, 582.
Goulding, R., and Robson, J. M. (1952). *Lancet*, **2**, 849.
Gowans, J. L. (1953a). *Brit. J. exp. Path.*, **34**, 35.
—— (1953b). Ibid., **34**, 195.
Hamilton R. R. (1953). *British Medical Journal*, **1**, 29.
Hart, P. D'Arcy (1946). Ibid., **2**, 805, 849.
—— Long, D. A., and Rees, R. J. W. (1952). Ibid., **1**, 680.
—— and Rees, R. J. W. (1950). *Lancet*, **2**, 391.
Helweg-Larsen, P. (1952). In *Acta med. scand.*, Suppl. No. 274, p. 330.
Hirsch, J. (1953). *Naturwissenschaften*, **40**, 490.
Hirsch, J. G. (1953). *J. exp. Med.*, **97**, 323, 327, 345.
—— (1954). *Proc 6th Int. Congr. Microbiol.*, 1953. In press.
—— and Dubos, R. J. (1952). *J. exp. Med.*, **95**, 191.
Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D. (1953). *Amer. Rev. Tuberc.*, **67**, 808.
Houghton, L. E. (1954). *Lancet*, **1**, 595.
Ilavsky, J., and Foley, E. J. (1953). *Proc. Soc. exp. Biol., N.Y.*, **84**, 211.
Jawetz, E. (1946). *Arch. intern. Med.*, **77**, 1.
—— and Merrill, E. R. (1953). *Science*, **118**, 549.
Jensen, K. A. (1949). *Acta tuberc. scand.*, Suppl. No. 21, p. 42.
Joiner, C. L., MacLean, K. S., Pritchard, E. K., Anderson, K., Collard, P., King, M. B., and Knox, R. (1952). *Lancet*, **2**, 843.
Kan, G. S. (1953). *Arkh. Patol.*, **15**, 13. Abstract in *Chem. Abstr.*, **1953**, **47**, col. 6526.
Kaplan, H. S., Speck, R. S., and Jawetz, E. (1952). *J. Lab. clin. Med.*, **40**, 682.
Karlson, A. G., and Feldman, W. H. (1953). *Amer. Rev. Tuberc.*, **68**, 26.
Knox, R., King, M. B., and Woodroffe, R. C. (1952). *Lancet*, **2**, 854.
LeMaistre, C., Tompsett, R., and McDermott, W. (1953). *Ann. N.Y. Acad. Sci.*, **56**, 772.
Lemonde, P., Panisset, M., Dobija, M., and Selye, H. (1952). *J. clin. Endocr.*, **12**, 973.
Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
—— —— and Perry, W. L. M. (1951). Ibid., **2**, 902.
—— and Spensley, P. C. (1954). Ibid., **1**, 645.
Long, E. R., and Ferebee, S H. (1950). *Publ. Hlth Rep., Wash.*, **65**, 1421.
Lovell, R. R. H., Goodman, H. C., Hudson, B., Armitage, P., and Pickering, G. W. (1953). *Clin. Sci.*, **12**, 41.
Lurie, M. B. (1950). *Amer. J. Med.*, **9**, 591.
—— Abramson, S., and Allison, M. J. (1949). *Amer. Rev. Tuberc.*, **59**, 168.
—— —— and Heppleston, A. G. (1952). *J. exp. Med.*, **95**, 119.
—— Zappasodi, P., Dannenberg, A. M., jun., and Cardona-Lynch, E. (1953a). *Ann N.Y. Acad. Sci.*, **56**, 779.
—— —— —— and Weiss, G. H. (1953b). *Trans. Stud. Coll. Phys., Philad.*, **21** (4th ser.), 93.
McDermott, W., Ormond, L., Muschenheim, C., Deuschle, K., McCune, R. M., jun., and Tompsett, R. (1954). *Amer. Rev. Tuberc.*, **69**, 319.
Mackaness, G. B. (1952). *J. Path. Bact.*, **64**, 429.
—— (1954a). *Amer. Rev. Tuberc.*, **69**, 690.
—— (1954b). *Brit. med. Bull.*, **10**, 100.
—— and Smith, N. (1952). *Amer. Rev. Tuberc.*, **66**, 125.
—— —— (1953). Ibid., **67**, 322
Magoffin, R. L., and Spink, W. W. (1951). *J. Lab. clin. Med.*, **37**, 924.
Marks, J. (1951). *British Medical Journal*, **2**, 1318.
Martin, A. R., and Stewart, G. T. (1950). *Brit. J. exp. Path.*, **31**, 189.
Mauer, H. (1952a). *Z. Tuberk.*, **101**, 51. Abstract in *Chem. Abstr.*, 1953, **47**, col. 8902.
—— (1952b). *Naturwissenschaften*, **39**, 502. Abstract in *Chem. Abstr.*, 1953, **47**, col. 10718.
—— and Finkeldey, W. (1952). Ibid., **39**, 503, 504. Abstract in *Chem. Abstr.*, 1953, **47**, cols. 9405, 10718.
—— —— (1953). *Z. Tuberk.*, **102**, 196. Abstract in *Chem. Abstr.*, **1953**, **47**, col. 8902.
Medical Research Council (1948). *British Medical Journal*, **2**, 769.
—— (1950). Ibid., **2**, 1073.
—— (1952a). Ibid., **1**, 1157.
—— (1952b). Ibid., **2**, 735.
—— (1953a). Ibid., **1**, 521.
—— (1953b). Ibid., **2**, 1005.
—— (1953c). *Lancet*, **2**, 217.
—— (1954a). *Thorax*. In press.
—— (1954b). Isoniazid Report No. 7. To be published.
Medlar, E. M. (1952). *Amer. Rev. Tuberc.*, **66**, 381.
Meyer, A. H., Kinsell, L. W., and Parsons, R. J. (1952). Ibid., **66**, 542.
Michael, M., jun., Cummings, M. M., and Bloom, W. L. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 613.
Middlebrook, G., and Yegian, D. (1946). *Amer. Rev. Tuberc.*, **54**, 553.
Mitchison, D. A. (1950). *Thorax*, **5**, 144.
—— (1954). *Brit. med. Bull.*, **10**, 115.

Morgan, T. E., Wanzer, S. H., and Smith, D. T. (1954). *J. Bact.*, **67**, 257.
Nègre, L. (1950). *Les Lipoides dans les Bacilles Tuberculeux et la Tuberculose*. Masson, Paris.
Ozeki, I. (1952). *Nagoya J. med. Sci.*, **15**, 176.
—— (1953). Ibid., **16**, 73.
Pagel, W. (1952). *Amer. Rev. Tuberc.*, **65**, 673.
Panà, C., Belli, N., and Perelli, A. (1952). *Lotta c. Tuberc.*, **22**, 303.
Raffel, S. (1950). *Experientia, Basel*, **6**, 410.
Rees, R. J. W. (1953). *Proc. roy. Soc. Med.*, **46**, 581.
—— (1954). *Brit. med. Bull.*, **10**, 104.
—— and Robson, J. M. (1950). *Science*, **112**, 790.
Rich, A. R. (1951). *Pathogenesis of Tuberculosis*, 2nd ed., pp. 287, 570. Blackwell Scientific Publ., Oxford.
Robinson, H. J., Mason, R. C., and Smith, A. L. (1953). *Proc. soc. exp. Biol., N.Y.*, **84**, 312.
Roche, P., jun., Cummings, M. M., and Hudgins, P. C. (1952). *Amer. Rev. Tuberc.*, **65**, 603.
Rosa, A., Olivo, R., and La Placa, M. (1953). *Nuovi Ann. Ig.*, **4**, 277, 282. Abstract in *Bull. Hyg., Lond.*, 1954, **29**, 202.
Schaefer, W. B. (1954). *Amer. Rev. Tuberc.*, **69**, 125.
Schmidt, L. H., Hoffmann, R., and Hughes, H. B. (1953). Ibid., **67**, 798.
Schwabacher, H., and Wilson, G. S. (1938). *J. Path. Bact.*, **46**, 535.
Siebenmann, C. O. (1953). *Amer. Rev. Tuberc.*, **68**, 411.
Singh, B., and Mitchison, D. A. (1954). *British Medical Journal*, **1**, 130.
Smith, D. G., and Waksman, S. A. (1947). *J. Bact.*, **54**, 253.
Smith, H. V. (1953). *Proc. roy. Soc. Med.*, **46**, 588.
—— and Vollum, R. L. (1950). *Lancet*, **2**, 275.
Solotorovsky, M., and Gregory, F. J. (1952). *Amer. Rev. Tuberc.*, **65**, 718.
—— —— and Stoerk, H. C. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 286.
Spain, D. M., and Molomut, N. (1950). *Amer. Rev. Tuberc.*, **62**, 337.
Staub, H. (1953). *Schweiz. med. Wschr.*, **83**, 531, 551. Abstract in *Bull. Hyg., Lond.*, 1953, **28**, 802.
Steenken, W., jun., d'Esopo, N. D., and Wolinsky, E. (1947). *Amer. Rev. Tuberc.*, **56**, 403.
—— and Pratt, P. C. (1949). Ibid., **59**, 664.
—— and Wolinsky, E. (1947). Ibid., **56**, 227.
—— —— (1948). Ibid., **58**, 353.
—— —— (1952). Ibid., **65**, 365.
—— —— and Pratt, P. C. (1951). Ibid., **64**, 87.
—— —— —— and Smith, M. M. (1952). Ibid., **66**, 194.
Suter, E. (1952). *J. exp. Med.*, **96**, 137.
—— (1953). Ibid., **97**, 235.
Svedberg, B. (1951). *Acta med. scand.*, Suppl. No. 254.
Szybalski, W., and Bryson, V. (1953). *Amer. Rev. Tuberc.*, **68**, 280.
Tucker, W. B. (1953). *Trans. 12th Conf. Chemother. Tuberc.*, p. 13. Amer. Veterans Admin., Washington.
Vorwald, A. J., Dworski, M., Pratt, P. C., and Delahant, A. B. (1950). *Amer. Rev. Tuberc.*, **62**, 455.
Weimer, H. E., Boak, R. A., Bogen, E., Drusch, H. E., Miller, J. N., Moshin, J. R., and Carpenter, C. M. (1953). Ibid., **68**, 31.
Weiser, O. L., Howard, O. P., and Dye, W. E. (1953). *Trans. 12th Conf. Chemother. Tuberc.*, p. 198. Amer. Veterans Admin., Washington.
Wells, A. Q., and Wylie, J. A. H. (1952). *Brit. J. exp. Path.*, **33**, 405.
Wilson, G. S., and Miles, A. A. (1946). In Topley and Wilson's *Principles of Bacteriology and Immunity*, 3rd ed., p. 425.
Woody, E., jun., and Avery, R. C. (1948). *Science*, **108**, 501.
Yegian, D. (1952). *Amer. Rev. Tuberc.*, **66**, 629.
Youmans, G. P., Doub, L., and Youmans, A. S. (1953). *Chem.-Biol. Coord. Centre (N.R.C., Wash.) Rev.* No. 4.
—— and Williston, E. H. (1946). *Proc. Soc. exp. Biol., N.Y.*, **63**, 131.
Zeichner, J., and Childress, W. G. (1953). *N.Y. St. J. Med.*, **53**, 1347.

THE DANGER OF ACCIDENTAL CARBON MONOXIDE POISONING

A REVIEW OF 100 CASES

BY

KEITH SIMPSON, M.D.

Reader in Forensic Medicine, Guy's Hospital, University of London

Every year in England and Wales some 400–500 cases of accidental poisoning by domestic coal-gas occur—a disquieting toll of life that has for many years been accepted as a natural risk of urban existence (Table I).

TABLE I.—*Registrar-General's Figures*

	1947	1948	1949	1950	1951
Males	170	166	195	158	215
Females	250	195	226	248	300
Total	420	361	421	406	515

Of the 1951 figure of 515 deaths, only 15 occurred at work; no fewer than 459 occurred at home, and some two-thirds of these involved elderly people—over 60 years of age—exposed to risk through forgetfulness or infirmity. Some means of reducing this carnage of accidental death must be sought, and this review of 100 successive cases from my records is designed to draw attention to: (*a*) common dangers inherent in present-day domestic gas usage; (*b*) other commonly unsuspected sources of CO pollution of air; and (*c*) the urgent need for adequate warning of danger, and for safety mechanisms in domestic apparatus.

Recognition of CO Poisoning

Although nothing new has come to light in recent years with regard to the treatment of CO poisoning, the importance of recognizing the condition and giving the appropriate treatment for it at the earliest possible moment cannot be emphasized too strongly. A low concentration of CO is easily overlooked, both in a stale atmosphere and in the body. The following review illustrates the ease with which the doctor may fail to recognize CO poisoning, though exercising reasonable care and maintaining an average vigilance for such matters in carrying out his everyday duties. Two examples will suffice.

In 1946 a family of three were found unconscious in the kitchen of a house at Watford; suspicion of foul play had arisen. A police constable left on guard for two and a half hours had become so obviously ill himself while waiting in the room—complaining of the stuffy atmosphere, of headache and nausea—that the possibility of CO poisoning from a vitiated atmosphere was at once suspected. The flue to a kitchen stove burning coke was found to be blocked by two sanitary pads which had been dropped through the top of the stove to burn but had been drawn into the vent. Samples of blood from the victims confirmed the absorption of carbon monoxide. A child already dead showed a figure of 44%: vomit inhalation had precipitated death at this low saturation.

In 1954 six persons—four children and two women—were found unconscious in a single bedroom at the rear of a flat at Waltham Cross. Poisoning with nicotine was suspected, as an empty tin had been found in an adjacent passage; but the atmosphere was thick with the stale fumes of gas, the window curtains were drawn, the window and door were closed, and a gas mantle and gas fire were found still burning. The fire had been lifted on to the mantelpiece to put it out of the way of the children, and it had thereby been deprived of the ventilation approved by the gas authority. All bodies were characteristically pink, and samples of blood revealed HbCO readings of between 20 and 42%. It was an astonishing fact that the persons first called to make entry—a police constable, C.I.D. officers, and a police surgeon—had not thought of CO as a cause for the catastrophe in spite of these pointers. Two of the victims recovered.

Such instances could be multiplied, and do, in fact, form a substantial proportion of the 100 successive cases reviewed here. A doctor called to an elderly person found dead under circumstances which raise no suspicion of violence may—and, it seems likely, commonly does—overlook the real substance of the case: CO poisoning may not be apparent in the first instance and may not be detected until the absence of disease and suspicion of poisoning from the colour of the blood have caused the pathologist to undertake a CO reading.

Age Incidence

In the sample series of 100 successive deaths from accidental exposure to CO taken for the purpose of this study the age incidence in decades was:

Age	No.	Age	No.	Age	No.
0–	6	30–	7	60–	17
10–	5	40–	5	70–	33
20–	3	50–	8	80–	16

The frequency of fatal exposure remains more or less the same until somewhere approaching the age of 60, after which a sharp rise to a level some four times that of any other period in life is reached. Of the 100 persons involved, 66 were over 60, and analysis of the circumstances showed that most of these cases—the figures are too small for more detailed breakdown in this respect—seemed likely to be attributable to increasing age and forgetfulness, senile decrepitude, or frank collapse.

The main causes were, in order of decreasing frequency: (*a*) trivial accidents with taps or burners, partly turned stopcocks, etc.; (*b*) ignorance of the importance of adequate

ventilation; blocked flues or vent pipes, especially from the bathroom; (*c*) fortuitous incidents reflecting defects in the supply, such as leaky apparatus, fractured mains, etc.; (*d*) exposure in consequence of collapse from natural disease, drunkenness, etc.

Many cases are presented to the doctor as unexpected sudden deaths, some of which he might feel tempted to certify, or to the pathologist as requiring necropsy to establish the cause of death, when, in fact, they revealed both natural disease and evidence of CO absorption. The ease with which the latter may be overlooked has already been referred to.

The sources of exposure from which the accidents arose are detailed in Table II.

TABLE II.—*Sources of Exposure*

Domestic supply not at fault		58
Age and infirmity: resulting in unlit or partly lit gas, and taps partly turned on or off	34	
Explosions after gas escapes from similar causes	2	
Natural causes not immediately fatal	11	
Drunkenness	6	
" with explosion after gas escape	1	
Accidental kicking-on, elbowing on, dousing (e.g., by fluids boiling over) of gas	4	
Domestic supply at fault		22
Defective piping or tubing, dirty or inefficient burning	12	
Fractured mains outside premises	8	
War operations causing fractured mains	2	
The " common meter " danger		3
Defective ventilation (domestic rooms, 3; bathroom vents (geysers), 6; coke-burning stoves, 3; fireworks, 1; running car, 2; amateur heating apparatus, 2)		17
Industrial conditions		2

The best way to illustrate the common dangers of a domestic gas supply which is " in a satisfactory state " on inspection is to select certain more common circumstances in fatal poisoning as a basis for comment.

Domestic Supply Not at Fault

Of the 58 cases coming within this category, 51 occurred as a consequence of aged, tottery, trembling hands half turning on or half turning off taps, turning on one jet and endeavouring to light the burner supplied by another, through fluid boiling over, through leaning on wall taps or kicking or pushing on floor taps (as by moving furniture)—a surprisingly large number (16) having, it was said at the inquests, no sense of smell. Blindness and deafness also contributed to fatalities.

Drunkenness has always added substantially to the risk of living; and, of course, to blunder drunkenly amid taps, fire-pokers, gas-rings, and other apparatus capable of turning on a highly lethal gas like carbon monoxide is to invite disaster.

The 11 subjects suffering from natural disease, the 36 merely old and infirm, the 7 who were drunk, and the 4 who leaned against taps or pushed furniture against them would not have died if there had been some spring return to the " off " requiring a ratchet or pin lock both to open the tap and to keep it open—rather as one does to lock a nut. One cannot pretend that all risk would be eliminated.

A man with pronounced coronary occlusion was found dead on the floor clutching a gas-bracket torn from the wall. The HbCO saturation had reached 38% only, death being due partly to this and partly to coronary occlusion.

An old recluse of 74 was found dead on the floor of her kitchen; one tap of the stove (supplying the oven) was on, but her food was still cooking, charred and by then dry, on a low ring flame. She was said to have had no sense of smell whatever. The saturation by HbCO was 63%.

A man of 60, under treatment for Hodgkin's disease, was found dead sitting in his chair by a gas-fire: it was unlit, and, some ventilation being present, no smell of coal-gas was reported. At necropsy the colour of the blood was thought to be surprisingly pink. Analysis showed a saturation of 40% HbCO, and a visit to the chair in which deceased sat made it clear that one only had to stretch one's feet to kick on a tap by the fireside: It was not of the drop type. The doctor in this case was prepared to certify death as due to Hodgkin's disease, but had not seen the patient for " about a month."

Faulty Domestic Supply

Where the domestic supply is at fault the consumer is, it must be admitted, as likely to be to blame as the supplier. The use of ancient, dilapidated, dirty apparatus, rotted rubber tubing, inefficient combustion systems, and the like is tantamount to risking death every day. In New York a big toll of life occurs each year from the use in small apartments of refrigerators which have been allowed to get into disrepair; the same carelessness plays a substantial part in the English figures.

A man of 53 (said to be without a sense of smell) was found dead on a lavatory seat. A gas copper lay in the room, supplied by a leaky rubber tubing which was fitted with the control tap *at the distal end*. The flow-meter showed a consumption of 21.7 cubic ft. (0.61 cubic metre) per hour instead of 5 to 7 cubic ft. (0.14–0.2 cubic metre) which would have been normal. The blood HbCO was 70%.

An old-fashioned geyser responsible for the death from CO fumes of a girl of 17 in her bath in London was found to be quite unable to burn efficiently the gas flow set for it. The room when closed accumulated 0.297% of CO. The girl had accumulated 52% HbCO by the time of her death, which may have been aided by coexistent oxygen shortage.

Mills and Smith (1950) have drawn attention to the necessity for adequate ventilation for instantaneous water-heaters in bathrooms of small capacity. Chilling and condensation add to the risk of incomplete combustion. Vitiation of the atmosphere is hardly avoidable in bathrooms (see below).

Fractured mains outside premises constitute a particularly lethal agent. Much of London's 4-in. (10-cm.) main piping was laid 50 to 60 years ago, and from cast rather than drawn pipes. Although of good-quality iron, they do not bend, and fractures are caused by violent ground movements such as occurred from war operations, or the slower subsidences of peacetime, especially in extremes of cold. Gas leaks from these may travel some distance between soil layers or around supply pipes and percolate into dwelling-houses, some of which have no domestic supply.

A night watchman of 63 was found dead in office premises at 6 a.m. He had had influenza three weeks previously and had not recovered fully. His death was assumed to be due to natural causes, but was reported for lack of recent medical attention. Necropsy revealed a faintly suspicious CO colour in the blood, and a sample revealed 29% HbCO. There was no fire or gas on the premises. Investigation revealed a 4-in. (10-cm.) main fracture 60 ft. (18 metres) away under the opposite side of the road. The myocardium showed some post-influenzal changes, explaining the low CO saturation, and it was subsequently said of the dead man that his recent illness had disturbed his sense of smell.

A woman of 73 and her daughter were found dead in bed on the ground floor of a house 110 ft. (33.5 metres) away from a fractured gas-pipe under the pavement. A hole had been burned in the 4-in. (10-cm.) main by fusion of an electric cable. Both had died in their sleep.

War operations and, in a recent catastrophe, flooding of the basement and lower floors of a house which put out a lighted gas-heater have resulted in the same fortuitous escape of gas with fatal results.

The Common Meter

Where several apartments, or a number of rooms in a single house, obtain a supply of gas through a common meter there is always a danger that someone, finding the supply exhausted, will insert a coin and thus start a flow of gas to rooms occupied by other persons unaware of the possibility.

A man of 68 returned drunk at midnight to his lodgings, shared by him with two other men having separate rooms—all supplied by a common penny-in-the-slot meter placed on the landing. He was found dead in bed next morning; the room was " filled with gas," and a gas-ring tap was found " full on." Two spent matches and a box lay near by. The two other lodgers had both inserted a coin to obtain a supply of gas for cooking between 7 and 8 o'clock that morning, and had left for work without ascertaining the whereabouts of the third man.

He, it was said, usually made himself a hot drink on retiring; but it appeared that he had found no supply of gas and had abandoned the idea *without shutting off the tap.*

A child of 10, left playing in a room lit by a gas-mantle whilst the parents went to the cinema, was found dead in bed at 6.30 o'clock next morning: gas was escaping from the gas-mantle bracket. It would seem that the gas had gone out during the night, and at 6 a.m. the mother had put a shilling in the slot of a downstairs meter on finding the supply exhausted. The saturation of the child's blood had reached 74% HbCO. No suspicion of foul play arose.

While there must always be a risk to joint users of a single meter who sleep with a mantle or fire burning, there can be no excuse for risking the lives of those living in a block of flats by a system which allows one householder to supply gas to others of whose movements and habits he may be ignorant. The "common meter" constitutes an obvious danger, and should be scrapped out of hand.

Defective Ventilation

Defective ventilation is, like defective apparatus, as likely to be fatal because of indifference to earlier warnings or danger, or to procrastination over repairs, as to lack of care in arranging for ventilation when the apparatus is installed. Gas radiators, stoves, refrigerators, and geysers should all have vents, for all are, in consequence of the risk of choking by dirt, of variations in the pressure of supply, of chilling and condensation, capable of imperfect combustion or of back-draughting CO into the atmosphere.

A man of 32 was found dead in his bath one Sunday morning. A geyser was on and hot water was running away from the overflow. He had drowned, but the colour of the livid stains and the saturation by CO of the blood (HbCO 37%) gave a clear indication of the cause. A starling's nest was found blocking the vent (which had no cowl or guard). A year previously his wife had been found unconscious in the same room—and a bird's nest had been removed from the same place, but nothing had been done to prevent a recurrence.

A man of 66 was found dead in the bunk he had fitted up in an air-raid shelter (dimensions 6 ft. 6 in. by 4 ft. 6 in. by 6 ft.—2 by 1.4 by 1.8 metres), the door of which had been closed by a heavy curtain. In order to provide heat he had arranged to burn a gas-mantle beneath a builder's brick propped across two other bricks. Condensation was marked, for the distance between the mantle and the transverse brick under which it burned was a bare ½ in. (1.3 cm.). The blood HbCO was 65%.

A man of 49 used a tin biscuit-box heated by a gas-tube burner for the same purpose in an Anderson-type shelter. He was found dead with a blood HbCO of 68%. A gas expert found that with a full supply of gas the flame became appreciably dulled from oxygen lack in 2½ minutes.

On two occasions deaths in the bathroom were said by the gas experts to have been due not so much to the fact that the geyser had failed to effect a full combustion as to the tendency for a strong wind from the "wrong quarter" to impede the easy escape of fumes or even to blow them back into the room. Instantaneous water-heaters whose consumption of "cold gas" is imperfect at the start should always have an efficient vent fixed.

The car in the garage and coke or other slow fuel-burning stove systems are better-known dangers, though again it is remarkable how commonly the need for free ventilation is overlooked.

A man of 53, recovering from a cold in the head, was found dead on the bed which he occupied as caretaker at school premises. A doctor who was called found no indication of the cause of death, but a police officer reported that the atmosphere was very close, since all the windows were shut and a stove burning coal and coke was still warm and appeared to be emitting fumes. The damper was closed and the draught door half open. The saturation of the blood was 58% HbCO. He had last been seen late in the previous evening, and had spent some 12 hours in a 35 by 15 by 7 ft. (10.7 by 4.6 by 2.1 metres) room in which there was no ventilation.

A single man of 34 was found, some 15 hours after being last seen putting his car away, lying prone with facial injuries on the floor of the garage close to the sliding door—which was latch-closed. The bonnet of the car was open and a tool-kit lay on the floor with tools, loose, close to the dead man's feet. The ignition was on, but though petrol was available the engine was not running. He was not found until search was made for him after failing to appear for work next day, by which time the atmosphere had cleared. The blood saturation of HbCO was 65%.

Industrial Sources of CO Poisoning

Industrial sources of CO are well recognized, and the possibilities of accidental exposure are so effectively controlled that, except for the sharp rise that wartime emergencies bring (see Registrar-General's annual figures for 1939–45), they contribute no significant part to the general incidence of accidental poisoning by CO. Events which are beyond ordinary calculations of risk are bound to occur, but they are comparatively rare.

A man of 58 went to inspect the lid of a water-gas production tank, the felt washers of which were giving trouble. He did not reappear, and search revealed him lying dead on the ground by the side of the tank, with minor bruising and abrasions of the face There was a 42% saturation of the blood by HbCO, and it became clear that in making the lid of an 18 by 12-ft. (5.5 by 3.7-metre) tank secure he had become exposed to an escape of water-gas. The composition of this was CO_2, 4.7; CO, 32.3; CNH_2N, 9.2; O_2, 0.1; H_2, 33.0; CH_4, 7.9; N_2, 12.2. It would follow that to be caught in an escape of this, even in ventilated premises, would be extremely dangerous—if not from CO, then from extreme oxygen lack. Sudden oxygen lack may in itself prove surprisingly quickly fatal.

Explosions and fire provide sources of accidental CO poisoning that do not come within the limits of this review, designed as it is to illustrate the disturbingly high annual death rate from the everyday use of domestic heating and lighting appliances. The apparent unconcern with which the gas authorities take this alarming annual toll of life is astonishing: the bovine calm with which the average householder accepts 400 to 500 deaths from accidental coal-gas poisoning each year reflects a remarkable lethargy of spirit.

A gas inspector gave evidence that "there was no defect in the installation" but, under examination, agreed that he had himself "inadvertently turned on" a rather loose gas-tap with his sleeve cuff in making an examination of the premises. This was precisely how an old lady had met her death—and how nearly a third of such deaths arise.

An energetic application to this simple mechanical problem is long overdue from those whose vast machinery and staff are concerned with the safe supply of coal-gas for domestic purposes: warning of the dangers of unlit gas, and of decrepit, dirty, unserviced, or inadequately ventilated apparatus should appear on every piece supplied, and the menace of the "party meter" must go without parley or delay. Accidents will always happen, but of the 100 cases reviewed here it would seem that some 70–75% could reasonably have been prevented. It is high time the problem was tackled and disposed of: it is not insuperable.

Summary

An analysis of 100 successive accidental deaths from carbon monoxide is given. Common dangers of domestic illuminating and heating apparatus, especially to the elderly and infirm, ill or drunk, are outlined.

The ease with which the general practitioner or the pathologist may overlook CO poisoning when the circumstances are not obvious or some adjuvant factor is operating indicates the need for vigilance. Low-saturation CO deaths are not uncommonly mistaken for natural deaths.

The very urgent need for tackling the problem of accidental domestic coal-gas deaths instead of accepting them as a misfortune is made clear by the large proportion of preventable deaths.

Reference

Mills, F. E., and Smith, F. C. (1950). *Report of the London and Southern Joint Gas Association.*

THREE CASES OF COLLAGEN DISEASE TREATED WITH CORTICOIDS

BY

D. G. RICHARDS, M.D., M.R.C.P.

Senior Registrar, Queen Elizabeth Hospital, Birmingham

Since Klemperer *et al.* (1941) first coined the term "diffuse collagen disease" it has become customary to group together as disorders of collagen tissue such seemingly diverse conditions as rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, diffuse sclerodermia, dermatomyositis, and polyarteritis nodosa. In all of these conditions there are widespread lesions in the connective tissues, and it is the extracellular components of the latter, the collagen fibrils and the intermediate ground substance, which are chiefly affected. It is because of the widespread network of delicate collagen tissues in the walls of small blood vessels, beneath the endocardium and the lining endothelium of synovial and serous membranes, that the collagen diseases may have many features in common. Therefore, extensive vascular lesions, arthritis, endocarditis, pericarditis, and pleurisy are all frequent manifestations. However, in spite of closely similar anatomical and pathological features, it has never been possible to demonstrate any aetiological relationship between individual members of the group. They are all distinct clinical entities, and diagnosis, even of the rarer types, often presents very little difficulty. Sometimes, however, patients suffering from the rarer collagen disorders may present with an extremely acute illness in which many of the more characteristic features may be absent or inconspicuous. It is in these instances that diagnosis may be very difficult.

The knowledge that many of these cases can be controlled by the administration of corticoid drugs has made early diagnosis of the greatest importance.

The case histories of three patients are presented below, to illustrate the difficulties in diagnosis in these very acute cases and to show how the administration of corticoids may preserve life, and how their continued administration may maintain reasonably good health for prolonged periods.

Case 1

A married woman aged 54 was first admitted to the Queen Elizabeth Hospital on July 16, 1951. She had been ill for four months with severe joint pains and heavy attacks of sweating. Two weeks before admission her symptoms became worse and she developed severe pain along the left costal margin.

On examination she looked very ill and had a temperature of 101° F. (38.3° C.). There was symmetrical swelling of the wrist-joints and of the small joints of the hands. The other joints appeared normal, but movements of the shoulders, ankles, and knees were painful. The spleen was just palpable, but the heart, lungs, central nervous system, and urine were all normal.

After a few days in hospital her condition deteriorated and she developed almost continuous pyrexia from 104 to 105° F. (40 to 40.6° C.). The pain in the chest became more severe and the respiratory rate rose to 40 a minute. Moist rales were heard over both lung bases, and there was clinical and radiological evidence of small bilateral pleural effusions. The pyrexia failed to respond to aureomycin and the patient was given salicylates.

After a few doses, however, there was a precipitate fall in temperature to subnormal levels and the patient became desperately ill with peripheral circulatory collapse and anuria. These symptoms lasted for 48 hours after the salicylate was discontinued, and then the temperature returned to its previous high level.

The agglutination reactions and blood cultures were negative. The blood showed an orthochromic anaemia (haemoglobin 84%) and a total white count of 5,700 per c.mm. (neutrophil polymorphs 79%). The sedimentation rate was high (54 mm. in the hour, Wintrobe), and estimation of the serum proteins showed a low albumin (2.2 g.%), and markedly raised gamma globulin (3.0 g.%) and fibrinogen (0.47 g.%).

The diagnosis on admission had been rheumatoid arthritis, but the severity of the illness, the marked pyrexia, and the inconspicuous joint changes, together with the appearance from time to time of a central facial erythema, suggested the possibility of disseminated lupus erythematosus.

Treatment with cortisone was begun on August 3, and 200 mg. was given daily for five days and then 75 mg. for a further 10 days. The temperature fell to normal within twenty-four hours and the patient's condition rapidly improved. However, on 75 mg. daily the temperature was not completely controlled, and rapidly returned to its previous level when the drug was discontinued. A.C.T.H., 30 mg., was then given daily by intramuscular injection, and this rapidly and completely controlled the pyrexia and all the symptoms.

After three weeks A.C.T.H. was discontinued and there was no relapse. The patient left hospital on October 3 and remained in good health until April, 1952, when pyrexia and joint pains returned. This relapse responded rapidly to a fortnight's course of A.C.T.H.

She remained well until December, when there was a return of severe arthralgia and high temperature. She was readmitted to hospital in January, 1953, and the symptoms were controlled on this occasion with cortisone. Relapse was rapid when the drug was discontinued, and since April, 1953, she has been on continuous maintenance therapy.

She is now on 100 mg. of cortisone daily, but pyrexia and joint pains return within twenty-four hours if any attempt is made to reduce this dose. On cortisone she enjoys reasonably good health and is able to do a full day's work looking after a grocer's shop. Her weight has increased by almost 3 st. (19 kg.) since treatment was begun in July, 1951.

Although symptoms are in abeyance the sedimentation rate is still raised (50 mm. in the hour, Wintrobe). The serum proteins remain abnormal, but less so than previously. The only abnormal clinical finding is a scaly red rash on the forehead, cheeks, nose, and chin. This has been present on and off for twenty years and was formerly regarded as acne rosacea. It was not in evidence during the initial acute illness, and tends to disappear during a relapse and to become more pronounced when the symptoms are controlled by cortisone.

The diagnosis of disseminated lupus erythematosus has been substantiated by the finding of lupus erythematosus cells in the peripheral blood. The differential sheep-cell agglutination tests gave a result in the lower range of significance (ratio 1 : 16). The direct Coombs test was negative.

Case 2

A girl aged 16 had enjoyed good health until July, 1952, when she began to complain of pain and stiffness in the feet and ankles, and later both knees, hands, elbows, and shoulders were affected. She was treated with phenylbutazone, but proved to be sensitive, and was admitted to another hospital with pyrexia, rash, and leucopenia. She remained as an in-patient for seven weeks and was discharged home in January, 1953. There was no improvement in the joint pains and stiffness, and her weight had decreased by nearly 3 st. (19 kg.) since the onset of the illness.

Her condition remained stationary until May, when she developed a sore throat and became acutely ill with severe pain in the central and left chest. She had difficulty in breathing, had marked pyrexia, and was vomiting. Three days later, on May 18, she was admitted to the Queen Elizabeth Hospital. She was desperately ill with a temperature of 104.6° F. (40.3° C.) and a respiratory rate of 54 a minute. There was generalized tenderness of the limbs and abdomen, and the slightest movement of the trunk or limbs caused severe pain. The small joints of the hands were slightly swollen, but all the other joints appeared normal. The skin of the fingers and backs of the hands was thickened, glossy, and unduly tethered to the underlying tissues.

The pyrexia and chest pain persisted, and two days after admission a pleural friction rub was heard in the right axilla, and shortly afterwards a pericardial friction rub became audible. A chest *x*-ray film showed a small left pleural effusion and an enlarged cardiovascular shadow strongly suggestive of pericardial effusion.

Investigations showed a marked orthochromic anaemia (red cells 3,080,000 per c.mm. and Hb 60%) and a total white-cell count of 13,400 per c.mm. (neutrophil polymorphs 83%). The sedimentation rate (Wintrobe) was 63 mm. in the hour. Agglutination reactions and blood cultures were negative, but the serum proteins were abnormal, the gamma globulin (4.2 g.%) and fibrinogen (0.74 g.%) being greatly increased. An E.C.G. showed flat T waves in all leads, but the P.–R. interval was normal. Lupus erythematosus cells were not found in the peripheral blood.

A diagnosis of "diffuse collagen disease" was made, and treatment with cortisone, 100 mg. daily, was begun on May 20. Progress was excellent, and the contrast between the patient's condition at the end of a week's therapy with that of her dangerously ill state on admission was remarkable. The generalized pains disappeared within a few days, but the temperature took eight days to reach normal levels. The pericardial and pleural friction quickly disappeared, but the tachycardia subsided slowly over a period of several weeks. Attempts to reduce the dose of cortisone below 75 mg. daily resulted in a recurrence of arthralgia and pyrexia. However, aspirin (60 gr.—4 g.—daily in divided doses), given as a "cortisone sparer," enabled the maintenance dose of cortisone to be gradually reduced to 37.5 mg. daily, without any further recurrence of symptoms.

The patient went home on August 12 after three months in hospital. She is still (March, 1954) on cortisone, 37.5 mg., and aspirin, 60 gr. (4 g.), daily, and is back at work as a clerk. She now gets only occasional joint pains, and has put on almost 3 st. (19 kg.) in weight since treatment with cortisone was begun.

The skin of the fingers and backs of the hands is thickened and inelastic, changes which were noted during the initial acute illness. These changes are now much more marked and are apparent, but to a less degree, in the skin of the arms, face, and upper chest. After leaving hospital it was discovered that the patient had noticed that for the past three years her fingers would become very blue on exposure to cold. It would seem that the Raynaud phenomenon is one manifestation of a diffuse sclerodermia. There has been, as yet, nothing to indicate involvement of the oesophagus, heart, or lungs, or of any other of the internal organs. Although the systemic symptoms are controlled the dermal changes have advanced in spite of cortisone therapy. Apart from slight stiffness of the fingers the sclerodermia has not given rise to much disability, but painful cracks and fissures have appeared in the atrophic skin over the finger-tips.

The sedimentation rate remains high and the serum protein levels are still abnormal, although the gamma-globulin fraction (3.7 g.%) is less elevated than formerly. The blood count has returned to normal. Typical lupus erythematosus cells have not been seen, but pre-lupus erythematosus cells are reported in the peripheral blood. The differential sheep-cell agglutination test gives a result outside the range of significance.

Case 3

A 53-year-old housewife has suffered from typical rheumatoid arthritis for the past 23 years. The condition affects practically all the peripheral joints, but especially the hands and knees. Early in 1953 there was a sharp exacerbation of the arthritis, which was treated with phenylbutazone. In June, 1953, she had improved enough to go on holiday, but shortly after returning she became ill with a high temperature, dry cough, and severe stabbing pain in the left chest. The condition did not respond to full courses of penicillin and chloramphenicol, and on August 7 she was admitted to the Queen Elizabeth Hospital. She was very ill, thin, and anaemic, with a temperature of 103° F. (39.4° C.) and marked tachycardia. The wrist-joints and small joints of the hands were swollen and deformed, with ulnar deviation. The knee-joints were slightly swollen, and movements of these joints and of the elbows, shoulders, and ankles were restricted and painful. The respiratory rate was raised to 30 a minute, but the lung fields were clear. There was no orthopnoea and no peripheral oedema or rise in venous pressure. The blood pressure was normal, but the heart was enlarged clinically. The sounds were normal and there were no murmurs. The spleen was not palpable, but the liver was very tender, the edge being easily felt four fingerbreadths below the costal margin. The central nervous system and urine were both normal.

The pyrexia continued, and after a few days the heart developed gallop rhythm and a loud pericardial friction rub was heard. A little later moist rales and a pleural friction rub were heard over the lower lobe of the left lung. The liver remained enlarged and tender, and the spleen now became palpable.

Investigations showed an orthochromic anaemia and leucopenia (red blood cells 3,240,000 per c.mm., haemoglobin 66%, and white cells 3,300 per c.mm.) A chest *x*-ray film showed clear lung fields, but the cardiothoracic ratio was increased (57%). Agglutination reactions and blood cultures were negative, but the sedimentation rate was raised 41 mm. in one hour (Wintrobe). Serum protein estimations showed a low normal level of albumin (3.5 g.%) and a raised globulin fraction (4.7 g.%).

At first it was thought that the condition might be an obscure form of hepatitis, possibly a toxic reaction to phenylbutazone. The patient was put on a high-protein diet with supplemental vitamins, and a further course of penicillin was tried, without, however, any effect on the pyrexia. A blood transfusion of 3 pints (1.7 litres) was given for the anaemia. After the development of pericarditis and pleurisy, the diagnosis was revised to "generalized collagen disorder," and this diagnosis was supported by the finding of lupus erythematosus cells in the peripheral blood.

Treatment with A.C.T.H. was begun on August 12. This was given in the form of A.C.T.H. gel, 60 units twice daily by intramuscular injection. After two days the dose was reduced to 40 units twice daily, and after a further three days to 30 units twice daily. There was a prompt fall in the temperature. Unfortunately, on August 21 A.C.T.H. had to be discontinued because of the development of considerable oedema and hypertension, and there was an almost immediate recurrence of pyrexia. After three days A.C.T.H. was restarted, but once more had to be discontinued because of oedema and hypertension. Cortisone, 100 mg. daily by mouth, was substituted on August 27, but, although the fluid retention and hypertension were less marked on this drug, the temperature was not so dramatically controlled as by A.C.T.H., and only gradually subsided to normal levels during the ensuing three weeks. During this time the patient's general condition gradually improved and the pleural rub disappeared. Small staphylococcal ulcers and abscesses developed over the lower back and buttocks, and were treated by a course of aureomycin. After seven weeks in hospital the patient improved sufficiently to be allowed up, but gallop rhythm and pericardial friction were still

audible from time to time. She went home on October 3 on a maintenance dose of 100 mg. of cortisone daily, and since then she has been seen for review at approximately monthly intervals. An attempt to reduce the daily dose of cortisone below 75 mg. resulted in a prompt return of pyrexia. Considering the severity of her recent illness, her condition now is very satisfactory and she is able to lead a fairly normal, but restricted, life.

On 75 mg. of cortisone daily the arthritis is less troublesome than it has been for some years, although the joints remain stiff and deformed. She is breathless on slight-to-moderate exertion and there is still some oedema of the feet and ankles. The blood pressure varies between 160/100 and 185/120 mm. Hg, and moderate tachycardia and cardiac enlargement are still present. A systolic murmur is audible at the cardiac apex, but the pericardial friction has disappeared. The lungs are normal both clinically and radiologically, but the spleen cannot be felt and the liver is much smaller than formerly. The urine has remained normal throughout the illness. The sedimentation rate remains high (33 mm. Wintrobe) and the serum proteins abnormal. The blood still shows a mild orthochromic anaemia, less marked than before (red blood cells 3,850,000 per c.mm., haemoglobin 80%), but the white-cell count is normal. The electrocardiograph shows a well-marked right bundle-branch block. Typical lupus erythematosus cells are still reported present in the peripheral blood. The differential sheep-cell agglutination test gives a result outside the range of significance.

Discussion

These three patients presented during very acute episodes of their illnesses. On admission to hospital they were all desperately ill with marked pyrexia and joint manifestations. All three developed pleurisy, and two had pericarditis. In each case the sedimentation rate was much raised, and the serum proteins were abnormal, with marked elevation of the gamma-globulin fractions. The blood counts showed an orthochromic anaemia and the total white-cell counts were low in proportion to the degree of pyrexia. Case 1 was at first thought to have severe rheumatoid arthritis, but the rather insignificant joint changes were not proportionate to the severity of the illness, and the appearance of a central facial erythema suggested a clinical diagnosis of disseminated lupus erythematosus. This was later substantiated by the finding of lupus erythematosus cells in the peripheral blood. Case 2 on admission to hospital was suspected of having acute rheumatic carditis and pericarditis, but the absence of valvular lesions, and the changes in the skin of the hands, led to a diagnosis of acute diffuse scleroderma. Case 3 had suffered from typical chronic rheumatoid arthritis for more than 20 years. The extremely acute episode with high pyrexia, pleurisy, and pericarditis suggested a diffuse collagen disorder. Lupus erythematosus cells were found in the peripheral blood, and their presence probably means that this is a case of systemic lupus erythematosus without the typical skin changes.

Reports in the literature on the use of corticoids in the treatment of the rare collagen disorders are not common and most refer to disseminated lupus erythematosus. In untreated cases the natural history is marked by spontaneous exacerbations and remissions. These fluctuations are unpredictable, and not infrequently a patient with chronic symptoms may suddenly become desperately ill with an acute crisis of the disease. Similar acute exacerbations may occur in the other collagen disorders. If untreated the prognosis is poor, although very occasionally these very acute attacks may subside without special therapy. The outlook is much more favourable if corticoids are used in treatment, and Dubois *et al.* (1952) believe that nearly all cases will respond so long as the hormones are pushed to the point of producing the features of a Cushing syndrome. The three patients whose case histories are described above were all admitted to hospital in an acute crisis, and were all so ill that a fatal outcome seemed likely. In each, response to corticoids was marked, and the hormones were probably life-saving.

In the long-term maintenance therapy of the collagen disorders the value of corticoids is less certain, and the variable course and duration of these disorders make evaluation of therapy very difficult. Jessar *et al.* (1953) reviewed 323 cases of disseminated lupus erythematosus not treated with corticoids (44 of their own cases and 279 collected from the literature) and found that approximately 20% survive for periods in excess of five years from the onset. Dubois *et al.* (1952) found the average life expectancy of patients with this disease to be 22 months. Bundick and Ellis (1951) reported 26 cases in which the average life span was four and a half years. In a report of nine cases of disseminated lupus erythematosus treated with cortisone, Johnson and Meyer (1952) conclude that this drug is usually effective in the control of symptoms and signs, but that relapse usually takes place on cessation of therapy. Tumulty and Harvey (1952) believe that patients with significant renal involvement are often made worse by treatment with corticoids.

Soffer and Bader (1952) treated 18 patients with disseminated lupus erythematosus with A.C.T.H. and/or cortisone for periods of from 3 to 20 months; of these, 6 had died at the time of their report and 12 are living, of whom 8 require maintenance therapy. They believe that, although no actual cures result, some patients may be maintained indefinitely in a state of remission by treatment with corticoids. Cohen and Cadman (1953) treated five cases of systemic lupus erythematosus with cortisone and A.C.T.H. for periods ranging from 8 to 30 months. The response was excellent in one case and satisfactory in the others. They considered that the more severe the systemic features of the disease the more dramatic is the immediate response to treatment and the more satisfactory is the long-term improvement.

The three cases reported in this paper have been on continuous cortisone therapy for 12, 10, and 7 months respectively, and all are maintained in reasonably good health. Cases 1 and 3 suffer an immediate relapse if an attempt is made to reduce the maintenance dose. Case 2 has remained on a steady dose of 37.5 mg. of cortisone daily since leaving hospital, and she also takes 60 gr. (4 g.) of aspirin daily as a "cortisone-sparer." In spite of cortisone the sclerodermatous changes are gradually becoming more pronounced, and recently trophic lesions have developed in the skin over the finger-tips. In all three cases the symptoms of the disease are suppressed, but the sedimentation rates remain high, and the serum protein abnormalities are still present. In each case there has been an improvement in the blood count during treatment, but in Cases 1 and 3 lupus erythematosus cells can still be found in the peripheral blood.

While on corticoids the patients have been subjected to regular clinical and biochemical review, and they have taken a low-salt diet with additional potassium in the form of potassium chloride, 6 g. daily by mouth. In only one patient have there been any important side-effects to therapy. Case 3 while on A.C.T.H. developed retention of sodium chloride and water, with hypertension severe enough to lead to discontinuance of the drug. On cortisone, these effects were less marked but still troublesome, and there is still considerable hypertension on a maintenance dose just sufficient to control symptoms. After three months on cortisone Case 3 developed severe pain in the back, and *x*-ray examination of the lumbar spine revealed generalized osteoporosis with partial collapse of lumbar vertebrae 2, 3, and 5. Cortisone may have been the responsible agent, or it may have aggravated a pre-existing menopausal osteoporosis. This patient has suffered also from recurrent staphylococcal abscesses, and it is possible that cortisone may be responsible for the delayed healing of these abscesses.

Summary

The case histories are described of three patients who were admitted to hospital during extremely acute episodes of generalized collagen disease. The dramatic effect of corticoid drugs in controlling the acute symptoms is illustrated.

Each patient has been maintained in reasonably good health by the continued administration of cortisone.

I am grateful to Dr. Ernest Bulmer for permission to publish Cases 1 and 2, and to Dr. A. G. W. Whitfield for Case 3, and to both for their encouragement and helpful criticism. I am indebted to the late Dr. A. L. Peeney, who undertook the pathological investigations.

References

Bundick, W. R., and Ellis, F. A. (1951). *Sth. med. J.*, **44**, 204.
Cohen, H., and Cadman, E. F. B. (1953). *Lancet*, **2**, 305.
Dubois, E. L., Commons, R. R., Starr, P., Stein, C. S., and Morrison, R. (1952). *J. Amer. med. Ass.*, **149**, 995.
Jessar, R. A., Lamont-Havers, R. W., and Ragan, C. (1953). *Ann. intern. Med.*, **38**, 717.
Johnson, S. A. M., and Meyer, O. O. (1952). *Amer. J. med. Sci.*, **223**, 9.
Klemperer, P., Pollack, A. D., and Baehr, G. (1941). *Arch. Path., Chicago*, **32**, 569.
Soffer, L. J., and Bader, R. (1952). *J. Amer. med. Ass.*, **149**, 1002.
Tumulty, P. A., and Harvey, A. M. (1952). *Bull. rheum. Dis.*, **2**, 17.

RESULTS OF A PLANNED ATTACK ON CARCINOMA OF THE VULVA

BY

STANLEY WAY, F.R.C.O.G.

Gynaecologist, Newcastle Regional Cancer Organization; Associate Surgeon, Gynaecological Department, Royal Victoria Infirmary, Newcastle-upon-Tyne

In 1939 during the course of a discussion at the Royal Society of Medicine on the treatment of carcinoma of the vulva, F. J. Browne suggested that since this was a fairly uncommon disease the results might be improved by concentrating all the cases in the hands of a few surgeons, who might thereby gain greater experience in handling the disease than if the cases were scattered in various clinics all over the country, usually in ones and twos.

My interest in the disease was aroused by my former chief, Clifford White, who suggested that a study of it might prove useful, especially as the incidence appeared comparatively high in Newcastle-upon-Tyne.

The more academic aspects of that study I have reported elsewhere (Way, 1951), but, briefly, the research showed that the previously poor results were due not only to lack of experience on the part of those responsible for its treatment but also to the fact that standard treatments at that time were based on unsound pathological and anatomical principles. The removal of the vulva was insufficiently wide in most cases to prevent recurrence, and the node dissections were not extensive enough to deal with the metastases.

As a result of this study, I devised the extended radical vulvectomy and node dissection which I have described elsewhere in full (Way, 1951), but which in brief consists of the complete removal of the vulva from the mons to the anus, extending deep enough to expose the pubic bones and their associated muscles; the excision of wedges of skin from the groins and saphenous regions with the underlying lymph nodes which remain undetached from the skin during the operation; the division of the inguinal ligament; and the removal of the external iliac lymph nodes as far as the bifurcation of the common iliac artery. The groin wounds are sutured, but the vulval wound is so wide that it has to be left to granulate. If the vulval wound can be sutured then the cardinal principle of cancer surgery is violated and recurrence can be expected in a fair proportion of cases.

The first of these operations I performed rather in the nature of an experiment in 1941. The patient had involved nodes, and died nine years later of coronary thrombosis without recurrence of the tumour or metastases.

From 1943 onwards, with the help of my colleagues in the gynaecological and radiotherapy departments, all the cases seen in the centre were handled by me and were assessed for this radical operation; in addition, most of the cases occurring in the gynaecological departments of neighbouring hospitals, in particular the Newcastle-upon-Tyne General Hospital, were also referred. The early cases were all performed in the Royal Victoria Infirmary, but the serious bed situation created by the long stay of these patients necessitated the provision of beds specially for them, and these were provided by the Newcastle Regional Cancer Organization in their associated hospitals, where more than half of the patients described in this paper were treated. The unselfish attitude of my colleagues and the co-operation of the Regional Cancer Organization, both before and after the advent of the National Health Service, played a great part in the excellent results that have been achieved, but without the very great assistance and encouragement of Professor Harvey Evers, who was quick to see the advantages of and to encourage the establishment of a special unit for this type of case, and Mr. John Thurgar, who, in the most difficult time, handed over radiotherapy beds for the surgical treatment of these cases, this planned attack could never have been carried out.

This paper describes the results of 79 cases seen prior to March 31, 1949. A five-year follow-up is available on all these patients, and they represent an unselected group who presented themselves for treatment at Newcastle hospitals. The results are believed to be representative of what can be achieved in any large centre where these cases are concentrated in the hands of a medical and nursing staff who see enough cases to become conversant with the problems involved.

Operability Rate

The higher the operability rate of a particular surgical technique the more useful the operation becomes. Table I shows that in this series the operability rate was 83%, and

Table I.—*Operability*

Total Cases Seen	Refused Treatment	Considered Unsuitable For Radical Operation	Operated Upon
79	1	13	65 (83%)

this would appear to be reasonably satisfactory. With increasing experience—and I have now performed this operation more than 150 times—this can be increased, and were I faced with the same group of cases now I am sure that I could have successfully operated on even more of them. The causes of rejection are given in Table II. It will be noticed that most of the cases rejected because the tumour was too advanced survived only a short while, and were in most cases dying when I first saw them. It is doubtful whether I could do anything for this group even now, but cases of heart disease now present little difficulty if the operation is carried out in stages. Diabetes remains a serious problem owing to the fact that inevitable infection of the raw wound tends to make control of the diabetes exceedingly difficult. However, by staging the operation and by increasing the time interval between the stages much can be done for these patients. Age of the patient may

TABLE II.—*Rejected Cases*

No.	Cause of Rejection	Alternative Treatment, If Any	Result
1	Diabetes	Wide local vulvectomy	Died of gas gangrene from infected insulin injection
2	Severe asthma	" " "	Died at 4 years from heart failure. No recurrence
3	Age (81)	Local excision of tumour	Died 1 year. Local recurrence
4	Heart disease	Radium and local vulvectomy	Alive and well at 6 years
5	Tumour too advanced	None	Died at 8 weeks
6	" " "	"	" " 6 "
7	" " "	"	" " 9 "
8	" " "	"	" "11 "
9	" " "	"	" " 3 "
10	" " "	"	" "11 months
12	Tumour too advanced, diabetes, and age (85)	Diathermy coagulation	Died from diabetes in 1 month. Tumour still active
13	Heart disease	Radium; local excision; superficial node dissection	Died at 3 years. Heart failure. No recurrence

One patient, who refused treatment, died three years later with extensive local disease but no evidence of metastases.

necessitate staging the operation, and in some cases in which node involvement is extensive and a one-stage operation is imperative because there is too little margin of safety between the primary and the lymph nodes, age may be the deciding factor between operation and rejection.

Material

The age distribution (Table III) of all these cases was not different from that in other published series of this disease—52% of all patients were over the age of 60. Over the age of 60 the operability rate was 78%; under 60 it was 90%.

TABLE III

Age Group	Total Cases Seen	Treated	Positive Nodes	Rejected	Refused Treatment	5-year Survivors
0–20	0	—	—	—	—	—
21–30	2	2	0	0	0	2
31–40	3	3	1	0	0	3
41–50	10	9	2	1	0	9
51–60	23	20	9	3	0	13
61–70	34	27	8	6	1	19
71–80	5	4	1	1	0	2
81+	2	0	—	2	0	0
	79	65	21	13	1	48

Size of tumour *per se* was seldom an indication for rejection, although in the 13 rejected cases the average size of the tumour was twice that of the operated cases (30 square cm. as compared with 16 square cm.).

Involvement of urethra, vagina, and rectum was not a contraindication to operation. Removal of a large part of the urethra led to only temporary incontinence, and the anus was removed with the performance of a colostomy in four patients, three of whom survived five years. The largest tumour in the rejected group was 90 square cm. The largest in the operated group was 102 square cm. The smallest tumour operated on was 0.25 square cm. This patient had a mass of nodes in her left groin 204 square cm. in area. It had been incised six times in three months by her doctor, who mistook it for an abscess. She died at one year of a groin recurrence, the only groin recurrence so far in the whole series.

Node involvement *per se* was never a contraindication to operation, and one patient with nodes fixed to the inguinal ligament and ulcerating the skin was treated and, furthermore, became a five-year survivor. Rejection was almost always decided on a combination of advanced tumour, advanced age, and concomitant disease. There was no significant difference between the average size of the tumours in the node-free cases (16.5 square cm.) and those in the node-involved cases (15.5 square cm.).

More recently our material has consisted of even more advanced cases, many of which are coming to us from far afield, but our operability rate still remains at the level described in this series. We still see too many recurrent cases which have already been the victims of timid surgery before they reach us.

Results

An operation stands or falls by its results. The results of the treatment of carcinoma of the vulva by methods other than those described in this paper have been far from satisfactory. The five-year survival rate achieved in this clinic prior to this experiment was a relative five-year one of 26%. This figure is on an equality with those reported from other centres, with the exception of Taussig (1941), who in a smaller series of cases with an operation which was more extensive than any described up to that time reported a relative figure of 58%.

Table IV shows the absolute five-year survival rate for this group of cases—that is, the percentage surviving at five years out of all cases seen, whether they were treated or

TABLE IV.—*Absolute Five-year Survival Rate*

Total cases seen	79
Refused treatment	1
Total cases considered for operation	78
Total operations performed	65
Alive and well at 5 years	48 (61%)

not. This absolute figure of 61% is very much higher than other published relative figures. The relative five-year survival rate in this series—that is, the survivors out of all the cases operated on—is 74% (Table V).

TABLE V.—*Relative Five-year Survival Rate*

Total operations	65
Operative deaths	8 (12%)
Intercurrent deaths without recurrence before 5 years	5 (8%)
Deaths from cancer	4 (6%)
Alive and well at 5 years	48 (74%)

The influence of node involvement in cancer at any site is of great importance, since the results are always worse when the nodes are involved (Table VI). It may be argued that the node involvement (32%) in this series is not as high as it might be and therefore the results are influenced

TABLE VI.—*Node Involvement*

Total No. of cases operated upon	65
Nodes involved	21 (32%)
" not involved	44
Five-year Results According to Node Involvement	
Nodes not involved:	
Total cases	44
Alive and well at 5 years	38 (86%)
Died of intercurrent disease before 5 years	2
" " operation	4 (9%)
" " metastases	0
" " local tumour	0
Nodes involved:	
Total cases	21
Alive and well at 5 years	10 (48%)
Died of intercurrent disease before 5 years	3
" " operation	4 (19%)
" " metastases	4
" " local tumour	0

by this. There is no doubt that to some extent this is the case, and in our larger series the incidence of node involvement is 47%, but it should be pointed out that in this series 9 out of 21 patients with node involvement had their iliac nodes involved as well as the inguinal—that is, 43% of the node-involved cases. In our larger series this incidence of deep node involvement was found to be only 22% of all node-involved cases. With increasing experience, and making allowance for the rather higher proportion of widespread node involvement in this early series, I believe that the lower incidence of node involvement has not made a great difference to the results.

The relative five-year survival rate in the node-free cases of 86% is an excellent one by any standards, and the fact that no patient in this group died of cancer is extremely satisfactory. It does, however, raise the question whether it is necessary to remove the nodes. I have pointed out elsewhere (Way, 1951) the impossibility of being certain on clinical examination whether or not the nodes are involved, and the 48% survival when the nodes are involved leaves me in no doubt about the wisdom of removing the superficial nodes in all cases in which this is possible. The

survival rate in the node-involved cases is reduced to 48%, but here again only four patients died of cancer, and here also there were no local recurrences. Many of these operations were extremely difficult, and this is reflected in the high operative mortality. However, of the nine patients with deep pelvic node involvement two survived and are well, one at 10½ years and one at 6½ years. This may suggest that the removal of the deep nodes is not an important step in the operation.

At the time these cases were treated we had little knowledge about the incidence and pattern of deep node involvement and no way of knowing if this step in the operation was vital. As a result of a far larger series we now know that the anatomical spread of cancer of the vulva in the lymphatics is fairly regular, and that involvement of the deep nodes is seen in only about 15% of all cases. As a result of this and the development by Dr. Ruth Dearing (1952) of her rapid node-smear technique we now modify this part of the operation by exposing the external iliac nodes and removing the lowest medial node (the node of Cloquet) and the lowest lateral external iliac node. These are smeared and stained (this takes no longer than seven minutes) whilst the superficial nodes are removed. If the deep nodes are negative the inguinal ligament is not divided and no further dissection of the iliac region is carried out. If they are involved then we proceed as we did with all the cases in this series. The greatest advance of this technique is undoubtedly the wide excision of the vulval area, because we have had no local recurrences in this series up to five years.

Discussion

The results really speak for themselves. The operation is more complicated than difficult and does require constant practice. The nursing is very complex, and the technique requires a fair amount of ancillary help and experience, especially in cytology since the introduction of the modification described above. The experiment—it has long since ceased to be one so far as I am concerned—may be said to have paid a handsome dividend, and the results are more than gratifying. It would seem well within the scope of any large centre which is prepared to concentrate its material and study the pathological and anatomical features of this disease.

Summary

Owing to the comparative rarity of carcinoma of the vulva few people see sufficient cases to become very familiar with the problems concerned in its treatment.

After research into the causes of failure to cure the disease an experiment was tried in which all the cases in a wide area were referred to one surgeon, who applied a more extensive operation based on the lessons of the preliminary research.

The results of the treatment of 79 cases seen before March 31, 1949, are reviewed.

One patient refused treatment and 13 were considered unfit. The operability rate was 83%. The absolute five-year survival rate was 61% and the relative five-year survival rate—that is, the survival of all cases operated on—was 74%. When the lymph nodes were involved the five-year survival rate was 48% and when they were not involved it was 86%.

These figures are a great improvement on other published figures and it is believed that they are well within the reach of any centre which decides to pool its cases into the hands of a special team which will carry out a radical approach to the disease.

References

Browne, F. J. (1939). *Proc. roy. Soc. Med.*, **32**, 308.
Dearing, R. M. (1952). *J. Obstet. Gynaec. Brit. Emp.*, **59**, 385.
Taussig, F. J. (1941). *Amer. J. Roentgenol.*, **45**, 813.
Way, S. (1951). *Malignant Disease of the Female Genital Tract*. Churchill, London.

TREATMENT OF GOUT WITH H.P.C.

BY

D. N. ROSS, M.D., F.R.F.P.S.

Assistant Physician, the General Hospital, Newcastle-upon-Tyne

One feature of the revival of interest in the rheumatic diseases following the introduction of cortisone and A.C.T.H. has been the screening of a great variety of substances for evidence of a cortisone-like action on the collagen group of diseases. Among the therapeutic agents, old and new, which have been examined is a cinchoninic acid derivative—namely, 3-hydroxy-2-phenylcinchoninic acid (H.P.C.). In the U.S.A. Blanchard *et al.* (1950) reported promising results with H.P.C. in cases of acute rheumatic fever, chronic rheumatoid arthritis, and disseminated lupus erythematosus. In this country Rennie *et al.* (1951) found the drug of value in a small group of cases of rheumatic fever and scleroderma. This preliminary report suggested that a further investigation was justifiable, and in the summer of 1951 a small supply of H.P.C. was obtained for trial and was used in a few early cases of rheumatoid arthritis. The results were not dramatic, and it was felt that H.P.C., being a derivative of cinchophen, might be of greater value in the treatment of gout. Accordingly, the small supply was hoarded until suitable cases were seen, but, as often happens, no patient with typical gout attended for many months; then several cropped up within a few weeks.

To date, 12 cases have been treated with H.P.C., a bitter yellow powder compressed into white-coated tablets containing 250 mg. The initial dosage recommended by Blanchard *et al.* (1950) was 20 mg. per kg. of body weight daily, in divided doses, by mouth, with an equal amount of sodium bicarbonate to prevent gastric upset. The amounts used in the trial, and the results, are described in the case abstracts.

Case 1

A farm worker aged 58 had his first attack of gouty arthritis in 1947, when his left hand, feet, and ankles were affected; subsequent acute attacks led to progressive involvement of the knees, elbows, and shoulders. He was admitted to Harrogate Royal Bath Hospital for a course of physical treatment in 1950 and had colchicine therapy during several acute episodes, with moderate benefit. At home he experienced general deterioration and was readmitted in January, 1952, when he joined a test group of cases which were given A.C.T.H. by intravenous infusion. The first infusion contained 10 mg. of A.C.T.H., and his condition improved during the next seven days; the second infusion contained 20 mg. of A.C.T.H., and his arthritis was appreciably relieved for 24 hours. The following day he relapsed to his original state, and the next day he developed a typical acute attack of gout with extremely painful tender joints and constitutional upset with pyrexia. At this stage H.P.C. was given in daily doses of 2 g., and he improved rapidly, being able to walk within 24 hours; after six days he had made such good progress that the dose was halved, and he continued to do well on 1 g. daily for another eight days. At this point he developed a recurrence of pain in his knees when walking, and began to complain of some nausea and looseness of the bowels. These symptoms became more severe next day, but treatment had to be interrupted in any event, as the available supplies of H.P.C. had been used.

During the next 12 days he deteriorated very much, until a fresh supply of H.P.C. enabled treatment to be resumed.

Improvement was almost immediate, and he continued to do well for three weeks, after which recurrence of the mild diarrhoea with pruritus ani and the appearance of an itching facial erythema caused treatment to be interrupted.

A third course was begun, but this led to a recurrence of a more widespread rash, and treatment was again stopped. His skin condition cleared up quickly, but his gout returned in a moderately severe form and he was most anxious to continue with H.P.C., in spite of the risk of skin complications. In an attempt to uncover any psychological bias, he was given inert tablets similar in appearance to H.P.C. for a few days, but at the end of this time he was having an attack of acute gout with a plasma uric acid level of 11.5 mg. per 100 ml. Although this setback weakened his faith in H.P.C., he responded at once to genuine treatment, and after a three-weeks course he was fit enough to go home, very much improved in general.

Subsequent Progress.—During the next six months he had great difficulty in obtaining supplies of H.P.C., and his clinical condition varied accordingly. He was recommended to take 0.75 g. daily as a maintenance dose for periods of three or four weeks, with intervals as his clinical condition suggested; in fact, some intervals were longer, and he then deteriorated rapidly, but he always derived immediate benefit when treatment was resumed.

Over the complete trial period of nine months he had at least 210 g. of the drug without serious toxic reaction, and laboratory tests showed no disturbance of liver function, no progressive rise in his blood urea level, and a recurrent sharp depression of his plasma uric acid curve after the initiation or resumption of medication. He regarded the occasional diarrhoea and rash as trivialities compared with the great benefit which the drug produced, and he was convinced that for him it was superior to colchicine.

Case 2

A labourer aged 40 had his first attack of gout in 1940, when his left big toe became painful and swollen; later the left ankle was affected. Since then he has had recurrent bouts in the feet, ankles, and right shoulder. Previous treatment with colchicine had relieved his acute symptoms in a few days.

He was admitted to the Royal Bath Hospital with less acute but more constant pain in the feet, ankles, and right shoulder. There was no swelling, redness, or warmth in the affected joints, and movement was restricted only by pain. During the first month he improved steadily with physical treatment, but biochemical tests suggested that he might be heading for a flare-up of the classical type. Within the next few days this did in fact occur; the right ankle became acutely painful, swollen, and tender. H.P.C. therapy was begun at once with 1.5 g. daily; dramatic improvement occurred in the first 12 hours, and continued steadily during the next five days, at the end of which he was completely free from pain when at rest but still had some pain on movement of the affected joint. At this time he complained of an itching psoriasiform lesion of the neck and shoulders; he stated that this rash always broke out during an acute attack of gout. After seven more days' treatment he felt very fit in general and was entirely free from pain, both at rest and on movement. The daily dose was then reduced to 0.75 g. for a further five days, by which time he was perfectly fit and up and about all day. He had never before made such a rapid recovery. He felt that H.P.C. was much superior to colchicine.

Case 3

A male clerk aged 23 developed acute arthritis at the age of 17 and was treated for rheumatoid arthritis with gold injections, which had no effect. In 1949 he was admitted to the Royal Bath Hospital, where clinical and laboratory investigations established the diagnosis of "chronic tophaceous gout" with chronic nephritis and hypogonadism. He benefited to some extent from treatment and was able to go home, where he kept fairly well during the next two years. At the end of 1951 his condition deteriorated rapidly and he was readmitted for a course of physical treatment.

At this stage it was thought that he might benefit from H.P.C., and 2 g. was given daily. After two days he developed an itching erythema on the neck and forearms, which had been exposed to bright sunlight, but this cleared spontaneously within an hour. This complication recurred the next day, but the reaction to sunlight was noticed and thereafter he avoided direct sunshine. After eight days' medication, during which time the plasma uric acid concentration had fallen from 9.6 to 6.8 mg. per 100 ml., the dose of H.P.C. was reduced to 1 g. daily. Treatment was interrupted on the eleventh day because of a recurrence of itching of the skin. During this first phase his previous general improvement had continued, but when H.P.C. was withheld he began to deteriorate steadily. After a 10-day interval his plasma uric acid level had risen to 8.5 mg., so H.P.C., 2 g. daily, was resumed. After only three days, during which the blood urea increased from 77 to 110 mg. per 100 ml., the drug was withdrawn because of the patient's known impairment of renal function and the reported tendency of H.P.C. to produce azotaemia in some cases.

Case 4

A gardener aged 74 had suffered from recurrent attacks of gouty arthritis for 14 years but had been able to keep working as a gardener for most of the time.

He was admitted to the Royal Bath Hospital on March 6, 1952, with subacute arthritis affecting the hands and feet, which had multiple tophaceous deposits, and he seemed a suitable case for trial. H.P.C., 1.5 g. daily, was given and improvement began almost at once. After 12 days he developed some looseness of the bowels, associated with pruritus, and the drug was withheld for one day, being then resumed with a dosage of 0.75 g. During the next fortnight his condition deteriorated slightly, which suggested that he might not be getting quite enough of the drug. However, a return of the mild diarrhoea led to the treatment being interrupted for 10 days. He then had a general relapse, with a return of joint pain and tenderness, and H.P.C. therapy was resumed. Unfortunately, only two doses produced a recurrence of his diarrhoea, and the treatment was then stopped finally.

During this period the patient had a total of 30 g. of H.P.C. and his plasma uric acid levels ranged from 9.9 to 4.2 mg. The drug produced much improvement in his arthritic symptoms, but his alimentary tract was too intolerant of it to allow treatment to continue any longer.

Case 5

A farmer now aged 56 had sudden onset of pain, swelling, and redness of the metatarso-phalangeal joint of the left big toe in 1941. The condition settled down, but he had occasional recurrences during the next seven years. In 1948 he had an acute polyarthritis affecting the elbows, wrists, hands, and feet; this was improved by a course of physical treatment. Thereafter transient attacks of pain occurred in the hands until January, 1952, when he had another attack of acute polyarthritis, in which the shoulders, hands, knees, and right foot were involved.

This acute phase was still present when he was admitted to the Royal Bath Hospital, and in view of his history, the presence of a large tophus, and the biochemical findings a course of H.P.C. was started. He was given 1.5 g. daily for nine days, the dose then being halved because of a slight looseness of the bowels; this cleared up in three days and the larger dose was resumed. However, after two days' treatment a moderately severe diarrhoea with vague abdominal pain recurred, and, although these responded to symptomatic treatment, the dose of H.P.C. was reduced to 1 g. daily, on which he continued for another 25 days. Clinically, he made a steady improvement, and at the end

of the course of treatment he was up and about all day, with no joint pain or tenderness, and felt well enough to return to his farm.

Subsequent Progress.—During his first few days at home he developed a marked vesicular rash on his face, following exposure to bright sunshine, which would suggest some cumulative effect of H.P.C. administration. The rash cleared up spontaneously and his improvement was maintained during the next three months.

Case 6

A publican aged 58, who reported a family history of gout, had himself suffered from the condition for 11 years, with recurrent acute attacks about four times a year which responded favourably to colchicine. He was admitted to the Royal Bath Hospital at the beginning of an acute attack of gout in the left ankle, associated with a more chronic arthritis affecting the knees and the elbow, wrist, and fingers of the right arm. H.P.C. treatment was started at once with 1.5 g. daily. This brought a dramatic improvement within 24 hours, with great diminution of pain, tenderness, and swelling of the ankle, and less marked, but none the less definite, improvement in the condition of the other affected joints. After 10 days he developed an itching erythema of the face and hands, following exposure to bright sunlight for about half an hour. As he still had some pain in the feet when walking, it was thought desirable to continue with H.P.C., but the dose was reduced to 0.75 g. daily; however, this was not quite sufficient to suppress his symptoms, because he developed slight pain and tenderness of the affected ankle within a week. The dose was then increased to 1.5 g. daily, on which he improved and continued to make excellent progress during the next month. By this time his condition was so good that the dose was reduced to 1 g. daily, on which he continued to do well.

He was discharged home a week later, and continued to take 1 g. daily for the next two months. During this time he had occasional recurrences of the facial erythema on exposure to bright sunlight when gardening, but he himself decided to do his gardening when the sunshine was less intense. He had no difficulty with the rash until the third month, which was in midsummer, when he complained of some increased tingling of the skin of the face, irritated by shaving; on account of this the dose was reduced to 0.5 g., which he took at night. He continued to keep very well during the next two months, but the skin irritation then became rather troublesome and it was felt wise to stop the drug. He had had six months' continuous medication, with a total of 150 g. of H.P.C. During that time there was no recurrence of gout or of the more chronic arthritic symptoms, and he declared spontaneously that he had enjoyed better health than for many years; he also thought that H.P.C. relieved his gout much more quickly and effectively than colchicine had done.

Case 7

A commercial traveller aged 43, who had been a heavy beer-drinker for many years, developed his first attack of gout in 1943 and had recurrences of varying severity in the succeeding years. In 1949 he had an unusually severe attack, and was admitted to a hospital where colchicine treatment was given with good effect. He was prescribed a "rigid diet" and advised to give up beer-drinking. On this regime he had only minor recurrences for three years, but intercurrently suffered a coronary occlusion with posterior cardiac infarction, which left him subject to anginal attacks on minimal exertion.

In 1952 he had another acute attack of gout, with general constitutional upset and fever, and involvement of the left foot and ankle. After a week's home treatment, which brought only slight improvement, he was admitted to hospital, where 1.5 g of H.P.C. was given daily. Improvement was immediate: within 48 hours he had no pain when at rest, and in a week he could walk freely within the limits of his cardiac disability. After another 10 days the dose was reduced to 1 g. daily, and his improvement continued; however, he developed a facial rash which became so irritating that the drug was stopped after a month. He remained well for about a fortnight, during which time his skin cleared; but thereafter he began to feel rather depressed and thought that "the gout was starting up again."

A typical flare-up in the left foot followed, and 1.5 g. of H.P.C. was given daily with dramatic improvement; three days later the dose was reduced to 1 g. daily, and was kept at that level for a month, with no further complication. The daily dose was then reduced to 0.5 g., and the patient went on holiday for a month in high spirits. At the end of this period he was seen as an out-patient, and reported favourably, but 14 days later he had a mild recurrence in spite of the continued administration of H.P.C. It was then presumed that the maintenance dose was too low, but in view of our experience with other cases it was felt desirable to prescribe higher doses only on the occurrence of an acute attack or when premonitory symptoms appeared.

Case 8

This patient was a company director aged 67. There was a strong history of gout on both sides of the family: his mother had severe gout and so had his father's brother; in addition, a deceased brother of the patient had also suffered from the disorder. The patient had a 30-years history of the disease, with attacks of varying frequency and increasing severity.

He was admitted to hospital with acute arthritis of the left elbow and wrist, and was ill and feverish. H.P.C. therapy was begun with 2 g., and improvement occurred in 12 hours. The dose was reduced to 1.5 g. daily for the next seven days, during which time his improvement was remarkable in comparison with his previous experience, and then it was again reduced to 1 g. daily. After a few days he felt so well that he was allowed to go home to see to some urgent matters of business; he reported as an out-patient a week later, when he stated that his progress had been excellent. On this occasion, however, a slight facial erythema was observed, although he had not noticed it. He was anxious to continue on treatment, as he found that he was able to carry on his business without impediment, and the daily dose was not altered. When seen again in 10 days he had remained very well, but the facial rash had become vesicular and irritating, so continuous treatment was stopped.

During the next three months he was seen regularly, and remained well. He reported that he had had several "warnings" of impending gouty attacks, but he had found that two to four days of intensive treatment with H.P.C., in doses of 1.5 g. daily, prevented these from developing into major episodes. He was able to continue an active business life, and felt that he had an effective remedy for his gout, which previously had incapacitated him for weeks at a time.

This patient had a mild degree of impairment of renal function, and his blood urea level rose during the first week of treatment from 58 to 72 mg. per 100 ml.; at the end of the second week, when the dose of H.P.C. was lower, the reading was 46 mg. per 100 ml.; in the succeeding months, when he had no continuous therapy, his blood urea levels were 52 and 60 mg. per 100 ml.—probably his "normal" figures.

Case 9

A publican aged 51 had 20 years' history of typical gout, beginning in the great-toe joints; attacks occurred about once a year at first, gradually becoming more frequent and more severe, and extending to other joints. In the past five years the bouts had become much worse, lasted longer, and left chronic arthritic symptoms.

He was admitted to hospital with acute gouty arthritis of both feet, the right ankle, and both knees; H.P.C.

therapy was begun at once with 1.5 g. daily, which produced considerable improvement within 24 hours. After 48 hours he developed diarrhoea and the dosage was reduced to 0.75 g. daily, on which he continued to improve during the next fortnight. At this stage he had a slight irritation of the face after shaving, and the dose was reduced to 0.5 g. daily for another fortnight. He then developed a mild attack of gout—at a time when I was absent on holiday, so that no alteration in dosage was made. This was much less severe than his "usual attack," lasting only four days, compared with the previous average duration of 10 to 14 days. When I saw him again 14 days after the attack the skin lesion had become more serious, with vesiculation and pustulation. In view of his improved clinical condition H.P.C. treatment was stopped and he went home 10 days later, fully ambulant and completely free from pain. He had been treated previously with colchicine, and was convinced that H.P.C. was a more effective rapid remedy. Although he had a chronic renal lesion, his blood urea level did not exceed 28 mg. per 100 ml. at any time during treatment, and there was no evidence of hepatic dysfunction in spite of the fact that his bowel and skin were irritated early and severely by the drug.

Case 10

A business man aged 61 had his first attack of gout 12 years previously, when both great toes were affected. In the intervening period he had recurrences at varying intervals, and in the past two years his left knee and right wrist were involved, particularly after strenuous exercise in which these joints were in play. When first seen he had acute arthritis of the right wrist and was prescribed H.P.C. in daily doses of 1.5 g., which produced much improvement in two days. After another week he felt so well that he resumed active work in his garden, but this provoked some pain and swelling of the feet, in spite of continuous medication. His feet improved during the next five days, but he then developed an itching erythema of the face and hands, so the daily dose was reduced to 1 g. This level was inadequate, for he had a mild attack of gout in the succeeding week, and although this cleared up much more quickly than usual he was unable to walk for a few days. After 14 days on the reduced dose he had a recurrence of the facial rash, with vesiculation, and treatment was interrupted.

At this stage he was advised to take H.P.C. only when he felt that an attack was coming on, and to limit the dose to 1.5 g. daily for two or three days. In the following year he acted on this advice with good effect and was able to avoid any major episodes. After six months, however, he found that he had to take the drug for three days, whereas previously two days' treatment was sufficient.

In the period of continuous therapy he had 35 g. of H.P.C., but there was no evidence of hepatic disturbance as a result, although he had a history of "catarrhal jaundice" in 1928, which might have predisposed to liver damage if H.P.C. were hepatotoxic.

Two Further Cases

The following two cases were treated in Professor Hartfall's clinic at Leeds, and the summaries were kindly supplied by his senior registrar, Dr. Chandler.

Case 11.—A man aged 60 had his first attack 29 years ago, with recurrences every year or so, affecting the feet primarily but more recently involving the knees and wrists. He had very little chronic disability, but there was associated radiological evidence of Paget's disease, which caused him some pain, although the current symptoms were articular and undoubtedly the expression of gout. On admission his blood uric acid reading was 7.2 mg. per 100 ml., and he was given 2 g. of H.P.C. daily. His blood uric acid levels were estimated daily and showed a rapid fall under the influence of treatment, and by the fifth day the reading was 4 mg. per 100 ml., associated with complete relief of symptoms. He was sent home on a daily dose of 1.5 g., and this was maintained for two months, when it had to be interrupted because of a vesicular facial rash. During the next three months his condition deteriorated in spite of colchicine therapy, and in January, 1953, H.P.C. treatment was resumed with daily doses of 1.5 g., which gave complete symptomatic relief.

Case 12.—A man aged 77 had 10 years' history of gout, which began in the ankles and gradually became more active and generalized. He was seen with acute arthritis of the hands and ankles, and H.P.C. therapy was started with a daily dose of 2 g. with considerable benefit. He was sent home on a daily dose of 1.5 g., on which he continued to do well during the next two months: thereafter he was given 0.75 g. daily on alternate weeks, and remained well during the subsequent four months.

Commentary

In the early cases H.P.C. was given in fractions at 0, 1, and 2 hours after breakfast, as recommended by the American workers. However, the incidence of diarrhoea shortly after the ingestion of the tablets led us to try more normal hospital methods. The drug was then given in divided doses after the main meals, two, three, or four times daily according to the total amount, and this system caused less alimentary upset.

In their pharmacological studies, based on animal experiments, Marshall and Dearborn (1950) conclude that "neither acutely nor chronically does H.P.C. appear to be a very toxic substance." In our series of cases, summarized in the table, there was no major toxic incident, but minor reactions were frequent. Alimentary upsets, in the form of vague nausea or diarrhoea, were largely avoided by giving the drug in divided doses throughout the day, always with an equal amount of sodium bicarbonate. Skin reactions were very troublesome and there was an element of photosensitivity in the early appearance of the usual erythema: the later reactions, characterized by vesiculation and sometimes pustulation, were probably due to excretion of the drug in the sweat, and were most severe in warm weather. (Incidentally, it was noticed that in the warm weather, when there was increased sweating and diminished output of urine, acute attacks of gout were more frequent.) Renal disturbances were not serious, with the exception of Case 3, which was unusually severe and complex, and the frequency of micturition reported by Simson and Bunim (1951) and Ehrlich *et al.* (1952) was not complained of by any patient. However, it would seem wise to have frequent estimations of the blood urea level of any patient receiving medication for a long period. Liver dysfunction was not found in any case in the group and,

H.P.C. Therapy: Summary of Dosage and Toxic Reactions

Case No.	Duration of Treatment (Days)	Total Dose of H.P.C. (g.)	Plasma Uric Acid: Range during Period (mg./100 ml.)	Toxic Reactions		
				Skin	Alimentary	Renal
1	270	210	14·4–4·8	Erythema. Vesiculation	Nausea. Diarrhoea. Pruritus ani	
2	17	22	7·8–5·1	Psoriasis		
3	24	25	9·6–6·8	Erythema		Azotaemia
4	36	30	9·9–4·2		Diarrhoea. Pruritus ani	
5	40	44	6·9–3·8	Vesiculation	Diarrhoea	
6	180	150	7·5–2·8	Erythema		
7	120	95	7·0–1·8	„		
8	27	32	6·1–2·1	Erythema. Vesiculation		(?) Azotaemia
9	44	28	8·3–4·7	Erythema. Vesiculation Pustulation	Diarrhoea	
10	28	35	6·5–2·4	Erythema. Vesiculation		
11	66	99	7·2–4·0	Vesiculation		
12	190	155	Initially 6·0			

although the limitations of liver function tests are realized, it seems reasonable to conclude that the absence of any hepatic complication, in patients treated 12 to 18 months previously, suggests that H.P.C. has no marked hepatotoxic effect, in spite of its relationship to cinchophen. In fact, a careful and critical review by Hueper (1948) mentions that cinchophen, when used in the treatment of gout, was much less toxic than was commonly supposed.

Conclusions

As the case summaries show, H.P.C. is an effective agent for the treatment of acute gout, and patients who had been treated earlier with colchicine were convinced that the new drug was more effective, in that it relieved their symptoms more quickly and more completely. In cases of the more chronic type of gouty arthritis, H.P.C. again proved effective, but its action was slower and less dramatic: it would appear that about a month's treatment is necessary in such cases before appreciable improvement occurs, but that, thereafter, acute episodes may be treated or prevented by a few days' intensive therapy. Although continuous treatment may be given for longer periods without major complications, the frequent occurrence of skin lesions makes any form of maintenance therapy impracticable, in spite of the fact that a severely affected patient may prefer an irritating rash to acutely painful joints.

Summary

Clinical trials of H.P.C. (3-hydroxy-2-phenyl-cinchoninic-acid), a derivative of cinchophen, in 12 cases of acute gout or chronic gouty arthritis have given satisfactory results. No major toxic effects complicated treatment, but minor reactions were common, involving particularly the skin: for this reason, it is recommended that this form of medication should be reserved for short-duration treatment of acute episodes, or for prophylactic treatment in patients in whom premonitory symptoms occur.

This investigation was conducted during my tenure of a Research Fellowship in Rheumatism of the University of Leeds and Royal Bath Hospital, Harrogate, and I am indebted to the physicians of the latter institution for access to the cases described, and to Professor S. J. Hartfall for facilities at his clinic in the General Infirmary at Leeds. It is a pleasure to record my thanks to Mr. R. Moffett, chief laboratory technician of the Rheumatism Research Unit of the University, for the many necessary biochemical investigations which he carried out so carefully and willingly. Generous samples of H.P.C. were provided by Herts Pharmaceuticals Ltd., through the good offices of Dr. D. McAnally.

References

Blanchard, K. C., Harvey, A. M., Howard, J. E., Kattus, A., Marshall, E. K., Newman, E. V., and Zubrod, C. G. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 50.
Ehrlich, M. E., Berkowitz, S., Carp, S. G., Soblen, R., and Steinbrocker, O. (1952). *N.Y. St. J. Med.*, **52**, 227.
Hueper, W. C. (1948). *Medicine, Baltimore*, **27**, 43.
Marshall, E. K., and Dearborn, E. H. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 36.
Rennie, J. B., Milne, J. A., and Somerville, J. (1951). *British Medical Journal*, **1**, 383.
Simson, J., and Bunim, J. J. (1951). *Amer. J. med. Sci.*, **222**, 523.

The *Yearbook of the Universities of the Commonwealth*, 1954, is 111 pages larger than the 1953 issue. It covers all the university institutions in the Commonwealth, giving general information and listing the academic staff and number of students. In this issue an attempt has been made for the first time to give for each university a statistical note of the number of its students who come from other countries. The statement of the history and functions of the Association of Universities of the British Commonwealth has been amplified. The alphabetical index of staff of the university institutions now comprises over 30,000 names. The *Yearbook* is published by the association at 36–37, Gordon Square, London, W.C.1, price £3 3s.

CAROTID-CAVERNOUS FISTULA

FIVE CASES WITH "SPONTANEOUS" RECOVERY

BY

JOHN M. POTTER, M.B., F.R.C.S.

Graduate Assistant, the Nuffield Department of Surgery, Oxford

Of the 15 cases of carotid-cavernous fistula recorded at the Radcliffe Infirmary, Oxford, during the years 1938–53, a spontaneous cure has occurred in five. Compared with other published series this is a high proportion, but in the three most recent cases the cures were not strictly spontaneous. These have been specially noted, as there were factors associated with their recovery—namely, carotid arteriography and hypotension—which might be called upon in future to encourage similarly satisfactory results. In three of the cases (two young men and a young woman) the cause was a severe head injury, but in two elderly women there was no apparent precipitating factor in the onset of symptoms. Particularly gratifying has been the absence of serious visual disturbance after recovery.

Case 1

A married woman aged 36 fell from her bicycle on October 19, 1944, and sustained a severe head injury. Her retrograde amnesia was 12 hours and post-traumatic amnesia four to five days. No definite skull fracture was seen on *x*-ray examination, but a right third nerve palsy with diplopia persisted and slight nominal dysphasia and continuing frontal headache were present. A month later she had an attack of vomiting, the headache was worse, the left eye protruded, the conjunctival vessels were distended, and considerable chemosis developed. The right eye soon followed suit. Visual acuity fell on the right from J 10 to J 18, and on the left from J 1 to J 12 (uncorrected). There was complete paralysis of the third and sixth cranial nerves on the right, and of the sixth on the left. A loud bruit was heard, particularly over the left fronto-temporal region, and this could be abolished by compressing the left common carotid artery. The degree of proptosis necessitated a left tarsorrhaphy two months after its onset. With rest in bed and sedation, some improvement in the proptosis and chemosis occurred, and the vision improved to J 4 on the right and J 6 on the left. The right third and sixth cranial nerve palsies also improved. During the period in hospital, digital compression of the left common carotid was attempted on several occasions but produced a feeling of faintness and paraesthesiae in the limbs. Ligation was therefore considered to be unwise. She was discharged from hospital five months after the injury with improvement both in the proptosis and of the bruit, which, although still present, was not very troublesome to her.

She continued much the same until July 20, 1945 (nine months after injury), when she felt faint while driving her car, and, after stopping it, did in fact lose consciousness. On recovering, she was given several alcoholic drinks and remembered little until she awoke the next day to find that the bruit had disappeared; the eyes had become very swollen again and she had a very bad headache. Examination revealed gross oedema and proptosis, on the right more than the left, and bilateral ophthalmoplegia which was almost complete. No bruit could be heard and the eyeballs did not pulsate. Steady improvement occurred, however, and she left hospital again two months after this episode, by which time the proptosis had almost subsided and her visual acuity, which had again been reduced, had improved to J 2 on the left and J 6 on the right. The right pupil was a little sluggish and there remained a complete

sixth nerve palsy on both sides. For the resulting diplopia a plastic operation was performed in November, 1945.

Improvement continued subsequently, and the patient was last seen in August, 1952, when she was quite well, having spent the previous six years hard at work with her husband on their farm in Canada. She had had only occasional slight headache and diplopia when tired. On examination the right pupil was larger than the left and immobile; and on the right, inward, upward, and lateral eye movements were defective but present.

Case 2

A married woman aged 58 had a sudden severe pain in the left occipital region and felt ill in August, 1947. The next day she noticed a "swishing noise" in the left temple, synchronous with her pulse; her left eyelid was drooped and swollen, and she had attacks of vomiting, which continued for several days. (Four years previously she had had a mild head injury without loss of consciousness, but this had been followed two months later by frontal headache with vomiting; the headaches had continued at irregular intervals up to the present episode.)

During three weeks' rest in bed the eye became less swollen, but the vomiting started again and the right eye also became red. On examination a month after the onset her blood pressure was found to be 190/90 and there was a loud bruit all over the skull, especially in the temporal region, and this could be abolished by left carotid compression. The fundi were normal; the left eye showed complete ptosis, external ophthalmoplegia, and marked proptosis, with swelling and congestion of the lids and conjunctiva. The right eye showed no proptosis, but there was slight swelling and oedema of the lids and congestion of the conjunctiva. There was no ophthalmoplegia on that side. Visual acuity on the left was 6/12 and J 16, and on the right 6/12 and J 8 (both corrected).

While in hospital she was given daily compression of the left common carotid artery, but this produced tingling of the right forearm after a few minutes, and was not tolerated for more than 10. Two months after the onset she had improved, her acuity being 6/12 and J 10 on the left and 6/4 and J 1 on the right (both corrected). Five months after the onset she had improved and there were no symptoms except the bruit. The left eye was still prominent and there was a little conjunctival oedema, but the ocular movements had improved.

In March, 1948 (seven months after the onset), she awoke one morning without the bruit, and it never returned. The left eye became a bit puffy but not as bad as it had been. The fundi were normal and the acuity was only slightly diminished. Her blood pressure was, however, 210/120. At the time of writing the patient is still alive, but suffers from the effects of hypertension, chiefly headache. There has been no return of the bruit, but there is still a tendency to diplopia and slight bilateral sixth nerve weakness.

Case 3

A married woman aged 72 noticed suddenly a pain in the left side of the face and head in November, 1952, and this was followed by "the noise of an engine" in her head. She vomited several times during the next day or two, and after three days her left eyelid drooped. She was seen nine days after the onset and was found to have a blood pressure of 185/90. A loud bruit could be heard over the left side of the head which could be abolished by left carotid compression. A complete left third nerve palsy was present but the fundi were normal. No proptosis, chemosis, or conjunctival reddening was noted.

Thirteen days after the onset a left internal carotid angiogram showed a large fusiform dilatation of the left carotid siphon. There was early filling of the veins in the left pterygoid fossa. This investigation was followed within a few hours by cessation of the bruit, which has not returned. For this she was very grateful, as the noise had been maddening her. She was last seen in January, 1954, when she was very well and had no diplopia.

Case 4

A man aged 33 met with a road accident in May, 1953. He sustained a severe head injury, a compound comminuted fracture of the right femur, and fractures of the right radius, ulna, carpals, and metacarpals. His retrograde amnesia was half an hour and post-traumatic amnesia 12 days, but no skull fracture was seen on the *x*-ray films. Proptosis of the right eye was noted, with some limitation of abduction and elevation. He was given blood for shock, his thigh wounds were sutured under general anaesthesia the same day, and skeletal traction was set up. Post-operatively he remained confused and there was also dysphasia. The right external ocular movements were restricted in all directions. There was also some right-sided hyposmia. A month after the injury he was still complaining of frontal headache and the right proptosis was still noticeable. During the following month there developed signs suggestive of a traumatic aneurysm in relation to the thigh wound.

Two months after the injury he said that he had had a noise in the right ear for about a month, and he still complained of mild but persistent right frontal headache. At this time conjunctival reddening was noted on the right, but the right eye, although prominent, was not pulsating. A bruit, audible in the right temple, was diminished by right carotid compression. The following day the right eye was seen to be pulsating. The visual acuity was J 1 on both sides, uncorrected. A right carotid angiogram three months after injury showed filling of the cavernous sinus in the arterial phase. Subsequently there was gradual but slight increase in the proptosis, and some chemosis, but he could close his lids comfortably and the bruit did not trouble him unduly.

Four months after injury, because no union was occurring, the femoral fracture was plated. During this operation massive bleeding occurred from a source which could not be identified, and this necessitated ligation of the femoral artery. Nine pints (5.1 litres) of blood was transfused and 8 more pints (4.5 litres) of packed cells during the next few days. A fortnight later it was necessary to perform a mid-thigh amputation, after which he became very shocked and his systolic blood pressure fell to 60 mm. and the diastolic pressure could not be recorded. Over 2 pints (1.1 litres) of blood was given by intra-arterial infusion, but just before this it had been noted that the proptosis was much less. The following day no bruit was audible and the proptosis had subsided to a large extent and was not pulsating. The prominent veins were no longer visible and there was no chemosis. There were, however, several haemorrhages in the right retina, one on the macula, although the visual acuity was J 2 (corrected).

Since then he has made good progress as regards his leg, and there has been no recurrence of the pulsating exophthalmos in the succeeding four months.

Case 5

A corporal aged 19 was injured in a motor-cycle accident in July, 1953. He sustained a head injury, and his post-traumatic amnesia was about 14 days. *X*-ray films showed a fractured base of the skull crossing the sphenoid bone; there were a right frontal haematoma, a right subconjunctival haemorrhage, and a periorbital haematoma. A week after the injury he complained of pain at the back of the right eye, and this showed some chemosis. The ocular movements were seen to be limited. Soon after he recovered from his amnesia he complained of a noise in the head. Two months after the injury a bruit could be heard over the right eye and frontal region, and could be reduced by right carotid compression. The right eye was prominent and a large vein crossed the chemotic upper lid. There was

pulsation of the eye, the movements of which were limited laterally, upwards, and inwards. There was some diplopia. Visual acuity was, however, J 1 on both sides, uncorrected. Bilateral hyposmia and a slight right lower facial weakness were also present. A right carotid angiogram showed filling of grossly dilated ophthalmic veins during the arterial phase. (It is to be noted that this case and Case 3 did not show actual filling of the cavernous sinus. This may indicate that the fistula led into one of the ophthalmic veins; but this is a fine arteriographic distinction, and these cases are therefore included in this series of carotid-cavernous fistulae.)

Twenty-four hours after the angiogram he noticed that the bruit had stopped and there was subsequently much improvement in the proptosis and chemosis. A later arteriogram showed the presence of a small aneurysm projecting from the cavernous portion of the internal carotid artery, but he remained free from symptoms and was well three months after the bruit had ceased.

Discussion

Much has been written on "pulsating exophthalmos," and it is a condition unusual enough to invite exhaustive review of the literature. This was done by Locke (1924), who considered all cases (588) on record up to that time, and was especially concerned with treatment. The catalogue was revised by Martin and Mabon (1943), who added 188 cases, and there have been many other writings on the subject, notably by Dorrance and Loudenslager (1934), Dandy (1937), Sugar and Meyer (1940), Holman *et al.* (1951), and Hamby (1952). "Pulsating exophthalmos" is not, however, synonymous with carotid-cavernous fistula, for about half the spontaneous cases of the former condition are due to other lesions involving the orbit, such as a vascular neoplasm, simple aneurysm, and encephalocele.

From the accounts given, therefore, it is possible to gain only a general impression of the result of the various forms of treatment and of the incidence of spontaneous recovery. Further, as Dorrance and Loudenslager (1934) point out, "the multiplicity of procedures used in most cases renders it almost impossible to present adequate conclusions in the form of a table." This is certainly true of the small series from which the cases already described were taken; and, in addition, two patients who were "cured" by internal carotid ligation died subsequently from haemorrhage. One, a traumatic case, had a fatal epistaxis six weeks later, when the internal carotid aneurysm ruptured into the sphenoidal air sinus (Cairns, 1942); the other, a case of spontaneous fistula, died from subarachnoid haemorrhage after 18 months. Dorrance and Loudenslager (1934) noted also that the cases occurring spontaneously usually suffered from advanced arterial disease and debilitating conditions common to those of advanced years; hence the higher mortality of either conservative or operative treatment in this group.

For cases occurring in the post-Listerian era of surgery, it is seen that internal and common carotid ligations are roughly of equal efficacy, curing approximately 50%, improving a further 30%, and bearing a mortality of about 6%. There is little information on the incidence of permanent hemiplegia, but it would seem to be about 7%. In a series of six cases in which a "trapping" operation was performed there were four cures but two deaths (Martin and Mabon, 1943).

Conservative treatment seems to result in about 12% cured, 30% improved, and 6% dead. These figures, when contrasted with those preceding, appear to offer little support for purely non-operative treatment, as Martin and Mabon contend; but it is unlikely nowadays that a case so treated would be denied surgery until it was too late. Indeed, most writers favour a preliminary period of conservatism before considering carotid ligation, in the hope that spontaneous cure will result, and that it will be assisted by such measures as rest in bed and courses of increasingly prolonged carotid compression. The small series of cases described in this paper lends support to such a regime.

The mechanism by which the fistulae closed in these cases is presumed to have been thrombosis, for in three there was temporary increase in the local symptoms and signs. In Case 2 there was no apparent cause for this. In Case 1 the cure came about in relation to a syncopal attack of some kind, and in Case 4 the relief was associated with hypotension due to loss of blood at amputation. It is interesting that it was in similar circumstances that the first recorded case of this condition was finally cured. Benjamin Travers in 1811 described "a case of aneurism by anastomosis in the orbit, cured by the ligature of the common carotid artery," which was one of the earliest carotid ligations with survival. The operation, on May 23, 1809, did not completely relieve the condition, but "on Saturday, 28th of October, she miscarried at the period of about ten weeks from conception. The hemorrhage [*sic*] was so considerable as to induce syncope, and leave her in a state of extreme debility. On the succeeding morning it was observed that the upper tumour was flattened and the pulsation had altogether ceased." Dandy would have regarded this as a spontaneous cure, for he considered that surgery was not curative unless the result occurred within two to three weeks. All this suggests that it might be beneficial, in the younger patients at any rate, to induce hypotension by some well-tried method, such as with hexamethonium bromide.

Cases 3 and 5 were cured following diagnostic carotid arteriography in which 42.5% and 35% diodone were used respectively for the antero-posterior and the lateral projections. The old lady (Case 3) was relieved within a few hours, and the young soldier about 24 hours later. It has been said that arteriography is rarely necessary to prove the diagnosis (Meadows, 1951), but these two cases suggest that it may have a desirable therapeutic side-effect and should be employed freely, perhaps with a stronger and more irritating solution of contrast media—for example, 50% diodone.

Because of their readiness to close, it might be believed that these were small fistulae. If so, then the suggestion sometimes made, that the intensity of the murmur is in proportion to the size of the fistula, is not correct; for most of these patients' bruits were loud ones.

In the first two cases, both of which reacted unfavourably to carotid compression, it was eight and nine months respectively before the fistula closed spontaneously. In the last three "assisted" cases the duration was from 13 days to four months. This suggests that it is inadvisable to lay down definite time limits for conservative therapy, provided the patients are not too troubled and are kept under careful observation.

Summary

From a series of 15 cases of carotid-cavernous fistula, five are described in which a cure, with preservation of good vision, occurred fortuitously with non-operative measures. This high proportion is emphasized.

Some methods of treatment and their efficacy are reviewed from the literature.

Two factors appearing to precipitate cure—hypotension and carotid arteriography—are discussed and their possible therapeutic roles suggested.

I am indebted to those who have allowed me to publish their cases: Mr. J. C. Scott, Dr. P. C. Mallam, the War Office, and particularly Mr. Joe Pennybacker, who has given much help and advice.

References

Cairns, H. (1942). *Lisboa méd.*, **19**, 375.
Dandy, W. E. (1937). *Zbl. Neurochir.*, **2**, 77.
Dorrance, G. M., and Loudenslager, P. E. (1934). *Amer. J. Ophthal.*, **17**, 1099.
Hamby, W. B. (1952). *Intracranial Aneurysms*. Thomas, Springfield, Ill.
Holman, E., *et al.* (1951). *Angiology*, **2**, 311.
Locke, C. E. (1924). *Ann. Surg.*, **80**, 1.
Martin, J. D., jun., and Mabon, R. F. (1943). *J. Amer. med. Ass.*, **121**, 330.
Meadows, S. P. (1951). In *Modern Trends in Neurology*, edited by A. Feiling, p. 430. Butterworth, London.
Sugar, H. S., and Meyer, S. J. (1940). *Arch. Ophthal., Chicago*, **23**, 1288.
Travers, B. (1811). *Med.-chir. Trans.*, **2**, 1.

MEASLES MENINGOENCEPHALOMYELITIS

BY

W. F. TWINING McMATH, M.D., M.R.C.P., D.P.H.

Physician-Superintendent, Neasden Hospital, London

Accounts of nervous disorders associated with measles, some of which were presumably meningoencephalitis, can be traced as far back as the beginning of the eighteenth century, according to the historians Comby (1935) and Rolleston (1937).

In this series 10 cases were encountered over a short period—three in the second quarter of 1951, from the Borough of Wembley, and seven between September, 1951, and June, 1953, widely distributed in the boroughs surrounding Neasden Hospital, a further two being from Wembley. The well-known protean character of the disease, and its tendency to occur in little groups, were well illustrated by these cases, but no light was thrown on the pathogenesis of the condition or on prevention and treatment, apart from the failure of A.C.T.H. to influence its course.

Notes of 10 Cases in Present Series

Case 1.—Female, 3½ years; severe measles. Severe encephalitis 5 days after rash; delirium, choreiform movements progressing over 10 days, coma 20 days. Retention of urine and incontinence of faeces. Flaccid quadriplegia. Plantar reflexes extensor and squint. Meningeal signs negative. C.S.F. normal. Complete recovery from paralysis, but personality changes marked: purposeless hyperkinesia, lacks concentration, plantar reflexes extensor.

Case 2.—Male, 5½ years; mild measles. Severe encephalitis 5 days after rash: lethargy, slurred speech, dysphagia, meningeal signs 5 days, left plantar extensor, motor aphasia. C.S.F.: lymphocytes 38. W.B.C. normal. Complete recovery in 3 weeks.

Case 3.—Male, 5 years; mild measles. Moderate encephalitis 3 days pre-eruptive: left facial palsy, meningeal signs 3 days. C.S.F.: lymphocytes 60, protein 40 mg. per 100 ml. W.B.C. normal. Recovery in 4 months.

Case 4.—Female, 6 years; mild measles. Moderate encephalitis 5 days after rash: lethargy, meningeal signs 10 days. Generalized hypotonia, plantar reflex extensor. Recovery in 5 weeks.

Case 5.—Male, 5½ years; moderate measles. Severe encephalitis 2 days after rash: meningeal signs 13 days; coma 14 days; cerebellar ataxia and behaviour problems. C.S.F.: lymphocytes 20, protein 80 mg. per 100 ml. W.B.C. normal. Recovery in 5 weeks.

Case 6.—Male, 20 months; mild measles. Severe encephalitis 3 days after rash: meningeal signs 4 days, convulsion, coma 2 days, cerebellar ataxia. C.S.F.: lymphocytes 80, protein 200 mg. per 100 ml. W.B.C. normal. Recovery in 5 weeks.

Case 7.—Female, 13 years; mild measles. Mild encephalitis 11 days after rash: meningeal signs 10 days. C.S.F.: cells 11,080 (90% lymphocytes). W.B.C. normal. Recovery in 18 days.

Case 8.—Male, 23 years; moderate measles. Mild encephalitis 3 days pre-eruptive: meningeal signs 9 days. C.S.F.: lymphocytes 10. W.B.C.: 4,400 (77% polymorphs). Recovery in 13 days.

Case 9.—Female, 3½ years; moderate measles. Very severe encephalitis 3 days after rash: meningeal signs 2 days; stupor 19 days. Quadriplegia, retention of urine. C.S.F.: lymphocytes 14. W.B.C.: 4,300 (65% polymorphs). Residual cerebellar ataxia and hypotonia. Aphasia. Behaviour problems. Given A.C.T.H. gel, 50 mg. daily I.M. for 8 days without benefit. Complete recovery from paralysis and almost so from ataxia, but after 6 months personality changes: stubborn, mentally retarded child.

Case 10.—Male, 5½ years; moderate measles. Very severe encephalitis 2 days pre-eruptive: meningeal signs 5 days. Delirium and coma 5 days. Incontinent of urine and faeces. C.S.F.: protein 200 mg. per 100 ml. W.B.C. normal. Given A.C.T.H., 10 mg. I.M. 6-hourly (3 doses) with no effect. Postural drainage and oxygen. Died of pulmonary oedema and anoxia. Post-mortem examination refused. Virus studies: positive complement-fixation reaction 1 in 80 to psittacosis, taken on 8th day, was considered to be a residual titre from a previous illness.

Incidence

It is difficult to determine whether the rising incidence recently recorded is real or is due to better diagnosis and reporting. Three of the present cases occurred in an area in which 795 cases of measles were notified in the same epidemic period—that is, an incidence of 1 in 285. In a series of 30 cases Hoyne and Slotkowski (1947) reported an incidence of 1 in 428, but a figure of the order of 1 in 1,000 more closely represents the overall incidence.

Diagnosis

The sudden onset of nervous symptoms in a patient making an apparently normal recovery from measles should suggest the possibility of meningoencephalitis, but all grades occur from slight or transient headache, drowsiness, and irritability, with or without initial vomiting. Its occurrence seems to be unrelated to the severity of the primary disease or to the presence of its characteristic complications, whether respiratory or gastro-intestinal. Some degree of fever is probably always present, but may be missed or attributed to other causes. Meningism is variable and usually of the mild form common in poliomyelitis, but may be completely absent, especially if the spinal fluid is normal. On the other hand, meningism is not uncommon in post-measles pneumonia, otitis media, and gastro-enteritis, especially in infants and young children. It may occur during the eruptive stage or in early convalescence (up to the fourteenth day from the onset), or even before the appearance of the rash (Cases 3, 8, and 10). These three patients had meningeal signs, one, suffering from delirium and coma, dying of pulmonary oedema and anoxia in five days. This early onset seems to be against the allergic hypothesis of aetiology. No cases appear to have been recorded before the onset of the disease or without the typical rash, in this respect unlike mumps.

Complement-fixation tests and isolation of the virus are so far inapplicable in forming a diagnosis, although Shaffer, Rake, and Hodes succeeded in growing the virus from the brain tissues of a fatal case as long ago as 1942. The coincidental prevalence of acute poliomyelitis may sometimes introduce an element of uncertainty, and occasionally the final diagnosis may depend on the subsequent development of mental and behaviour changes, in this respect resembling encephalitis lethargica.

Aetiology

In the cerebral disorders associated with infectious diseases and the prophylactic administration of their antigens, two varieties are differentiated:

(1) Post-infectious—that is, after virus diseases such as measles, rubella, smallpox, chicken-pox, and mumps, as well as after inoculations in which the antigen is living although attenuated, such as vaccination and rabies. The typical changes are diffuse demyelination and perivascular infiltration with small round cells, occurring in haphazard fashion more or less after the pattern of poliomyelitis. The damage is assumedly inflicted by the virus, probably a highly neurotropic variant, and, at least in the case of mumps, can be readily isolated from the cerebrospinal fluid.

(2) After inoculations in which the antigen is killed and usually modified in some way. *Haemophilus pertussis*

vaccines seem to be the commonest source of these accidents (Byers and Moll, 1948), but similar sequelae have been recorded after inoculation of diphtheria, typhoid, and other bacterial antigens as after the disease itself, again notably whooping-cough. These cerebral accidents are commonly regarded as allergic or protein-shock phenomena, the predominating changes being vascular thrombosis. The hypoxia accompanying severe paroxysms is regarded as an important factor in the causation of whooping-cough encephalopathy, which tends to leave permanent residua (Levy and Perry, 1948). The frequent occurrence of convulsions raises the question of an epileptic diathesis or like predisposition, or a trigger mechanism in cerebration which may be released by fever, from whatever cause.

Another theory, which receives less support than formerly, involves the existence of an unidentified encephalitis virus, which in some way is activated by these diseases or by the products of bacterial or viral metabolism. The sporadic appearance of "idiopathic" encephalitis lends some support to this theory (Brain and Hunter, 1929).

Prognosis and Treatment

The case mortality in the present series was 10% (the same as in Ford's (1928) series); delirium and coma were sudden in the fatal case and continued to the end five days later. Complicating features were terminal pulmonary oedema and the presence of psittacosis agglutinins in significant titre, but unfortunately a necropsy was refused. The higher fatality rates recorded by some workers were probably due in part to the omission of mild or doubtful cases; Hamilton and Hanna (1941), in their review of 241 from the literature and 44 of their own, recorded a case mortality of 20% and a residua rate of 40%.

There were no cases of permanent physical residua in the cases now reported, but two severe cases (Nos. 1 and 9) showed the worst sequelae—behaviour problems and maladjustment. The assessment of the latter is difficult, especially regarding the extent to which the environment perpetuates or improves the condition. The prognosis should always be guarded.

Treatment is largely symptomatic and anticipatory, involving oxygen and chemotherapy, especially when pulmonary or bulbar features are present. When cerebral oedema is suspected, concentrated albumin, plasma, or dextran may be given intravenously—usually three to four times the normal strength. Convalescent serum or gamma globulin may also be tried in the spreading forms of the disease; but little benefit can be expected in the ordinary forms as the initial cerebral assault appears to be maximal in degree and extent, the later changes being biochemical or reactionary and cumulative in their lethal effect. A.C.T.H. was given to two cases (one fatal) on the basis of an allergic aetiology, but seems to have had no effect on the course of the disease or in the prevention of residua, as the case which recovered became severely ataxic and paralysed, with pronounced personality changes.

Summary

Ten cases of measles meningoencephalomyelitis, three occurring in the pre-eruptive stage, were encountered in a localized area of North-west London between September, 1951, and June, 1953.

The average age of the patients was 5 years, the limits being 20 months and 23 years.

No correlation was observed between the incidence and severity of the disease and the character of the primary disease.

Of the three pre-eruptive cases, one was fatal. This early appearance, and in fact the lack of a fixed time-relationship to the rash, seem to be against the allergic hypothesis of aetiology; moreover, there was no eosinophilia.

Coma and severe paralyses are unfavourable features, especially if prolonged, but complete recovery may follow.

Predominantly meningitic forms tend to show pronounced fluid changes and encephalitic forms show slight changes, but a high pleocytosis is not incompatible with severe attacks.

Treatment is symptomatic and anticipatory, involving the use of oxygen and chemotherapy for severe forms. Immune sera and concentrated plasma given intravenously may turn the scale in selected cases, especially when cerebral oedema is a prominent feature. The failure of A.C.T.H. to influence the course of the disease (two cases) supports the virus rather than the allergic hypothesis of aetiology; but the drug was given rather late and in very severe cases.

The case mortality, 10%, equals the lowest recorded in a comparable series.

While physical residua were negligible or absent among the nine recoveries, two patients, both 3½ years old, showed undoubted mental and behaviour deterioration—in one so pronounced as to require institutional care.

References

Brain, W. R., and Hunter, D. (1929). *Lancet*, **1**, 221.
Byers, R. K., and Moll, F. C. (1948). *Pediatrics*, **1**, 437.
Comby, M. T. (1935). *Les Encéphalites aiguës post-infectieuses de l'enfance*. Paris.
Ford, F. R. (1928). *Bull. Johns Hopk. Hosp.*, **43**, 140.
Hamilton, P. M., and Hanna, R. J. (1941). *Amer. J. Dis. Child.*, **61**, 483.
Hoyne, A. L., and Slotkowski, E. L. (1947). Ibid., **73**, 554.
Levy, S., and Perry, H. A. (1948). *Amer. J. ment. Defic.*, **52**, 217.
Rolleston, J. D. (1937). *The History of the Acute Exanthemata*. London.
Shaffer, M. F., Rake, G., and Hodes, H. L. (1942). *Amer. J. Dis. Child.*, **64**, 815.

ANTAGONISTIC EFFECT OF A.C.T.H. AND CORTISONE ON THE ANTICOAGULANT ACTIVITY OF ETHYL BISCOUMACETATE

BY

JYOTI B. CHATTERJEA,* M.D.
Assistant Research Officer, Haematological Unit (Indian Council of Medical Research), School of Tropical Medicine, Calcutta

AND

LUCY SALOMON
Research Assistant, Blood Research Laboratory, New England Center Hospital, Boston

From the Ziskind Laboratories (Haematology Section) of the Joseph H. Pratt and New England Center Hospitals, and the Department of Medicine, Tufts College Medical School, Boston, Mass., U.S.A.

In agreement with the observations of Cosgriff *et al.* (1950) and Cosgriff (1951), we have noticed a higher incidence of thrombo-embolic complications during administration of A.C.T.H. and cortisone. While treating these complications with the anticoagulant ethyl biscoumacetate ("tromexan") we observed that patients on hormonal therapy would often need a larger dosage to maintain an optimum level of plasma prothrombin activity. On withdrawal of hormonal therapy the requirement of ethyl biscoumacetate decreased considerably.

Two patients were studied—one a case of idiopathic acquired haemolytic anaemia and the other a case of

*Working during the tenure of a Rockefeller Fellowship.

acute thrombophlebitis. The dosage schedule of A.C.T.H was 80 to 100 mg. daily, administered subcutaneously every six hours. After the full therapeutic effect had been obtained 20 to 25 mg. was given daily as maintenance therapy. From 150 to 200 mg. of cortisone was given either intramuscularly or orally, and the maintenance dosage was usually one-quarter of the maximum dosage. Ethyl biscoumacetate was administered in 300 to 1,200 mg. daily dosage, the exact requirement being determined in each case by plasma prothrombin activity. Plasma prothrombin activity was determined by a slight modification of the method of Quick (1945); activity of plasma prothrombin conversion factor (P.P.C.F., labile factor) by the method of Stefanini (1950); and the plasma fibrinogen level by a slight modification of the method of Quick (1942).

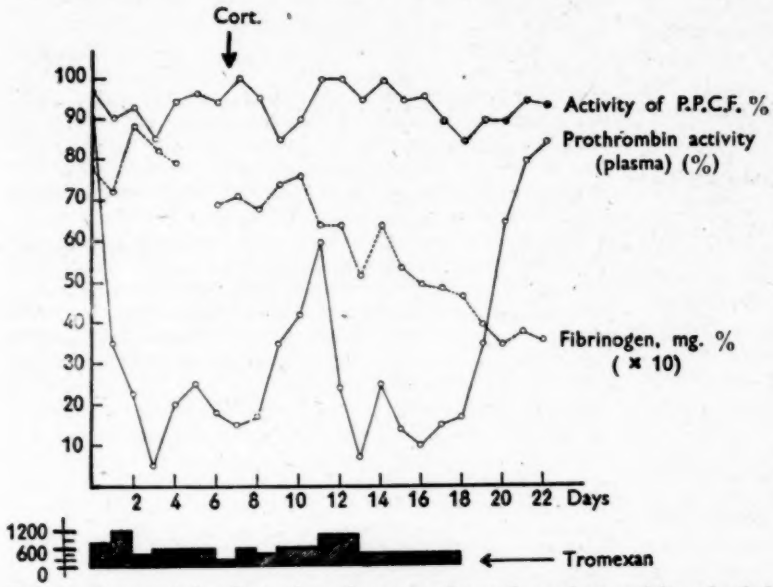


FIG. 1.—Antagonistic effect of cortisone on the anticoagulant activity of ethyl biscoumacetate is shown by the changes in the plasma prothrombin activity in a patient suffering from acquired haemolytic anaemia. Activity of plasma prothrombin conversion factor (P.P.C.F., labile factor) shows no significant changes. Plasma fibrinogen level, high before the institution of cortisone therapy, gradually came down to normal level on clinical and haematological improvement.

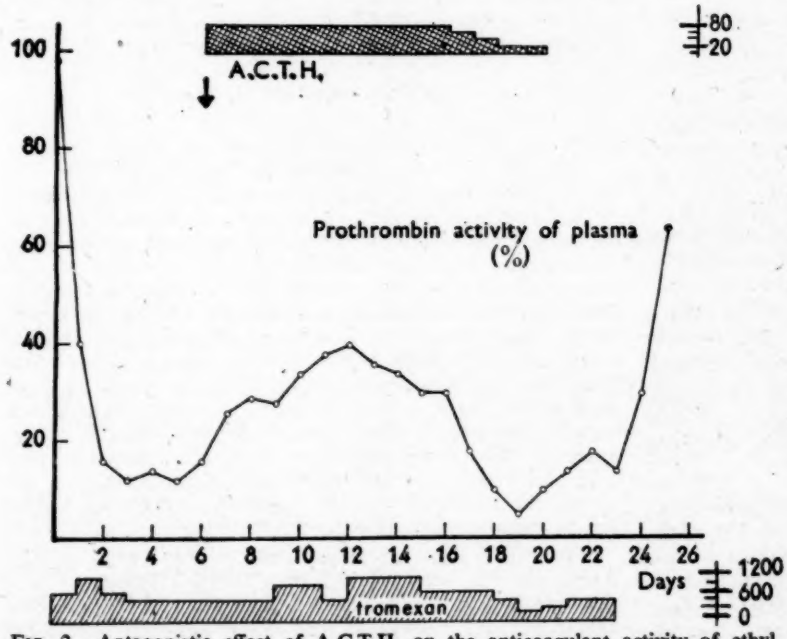


FIG. 2.—Antagonistic effect of A.C.T.H. on the anticoagulant activity of ethyl biscoumacetate is reflected in the behaviour of plasma prothrombin activity in a patient suffering from acute thrombophlebitis.

Results

The first patient developed thrombophlebitis during administration of cortisone. On the institution of anticoagulant therapy wide fluctuation of plasma prothrombin activity was noted, fluctuation being significant when compared with that seen in control patients not receiving concurrent hormone therapy. The behaviour of plasma prothrombin activity in the two cases studied is shown in Figs. 1 and 2. Fig. 1 shows the relevant data of a female patient with acquired haemolytic anaemia. Her serum contained easily demonstrable auto- and iso-red cell antibodies, and the Coombs test was positive. She developed a phlebothrombosis in her left leg while receiving 100 mg. cortisone. At this stage, cortisone was discontinued and anticoagulant therapy with ethyl biscoumacetate started. A satisfactory therapeutic level of plasma prothrombin activity was easily obtained. In view of a relapse of the haemolytic process, cortisone therapy was reinstituted on the seventh day of anticoagulant treatment. This was immediately followed by a rise in plasma prothrombin activity, and the dosage of ethyl biscoumacetate had to be increased to obtain an effective therapeutic level. Fig. 2 shows the data in a female patient with acute thrombophlebitis receiving ethyl biscoumacetate. After a satisfactory plasma prothrombin level had been obtained, A.C.T.H. therapy was started deliberately, to study the effect of the hormone on the plasma prothrombin activity. The immediate effect of the A.C.T.H. was to increase the requirement of ethyl biscoumacetate. An effective plasma prothrombin level could be obtained either by increasing the dosage of ethyl biscoumacetate or by decreasing the dosage of A.C.T.H.

Discussion

Our observations confirm the increase in the incidence of thrombo-embolic complications in the course of A.C.T.H. and cortisone therapy. The mechanism of this phenomenon is not clear. Reports on the effect of A.C.T.H. on the haemostatic process are conflicting. A.C.T.H. may cause temporary thrombocytosis both in the normal and in thrombopenic subjects (Koller and Zollikofer, 1950; Dameshek *et al.*, 1950; Rosenthal *et al.*, 1951). Cosgriff *et al.* (1950) observed acceleration of the venous clotting-time and of the heparin-retarded venous clotting-time, suggesting a state of hypercoagulability conducive to thrombo-embolic complications. Smith *et al.* (1950), on the other hand, found prolonged clotting-time and increase of heparin-like substances, suggesting an anticoagulant action of the hormone. McGraw *et al.* (1952) gave corticotropin treatment to 12 patients with phlebothrombosis or thrombophlebitis and cortisone to a similar patient. Along with subjective and objective improvement, they observed increased protamine titration values in three patients and significant reduction of prothrombin activity in nine. Fahey (1951), however, failed to detect any significant alteration of the coagulation time with A.C.T.H. in normal human subjects or in patients with hypo- or hyperadrenocorticism.

Although the mechanism is not clear, it is of considerable importance to be aware of this phenomenon, so that the dosage of ethyl biscoumacetate may be adequate to control thrombo-embolic complications during hormone therapy. Unless absolutely indicated for their known specific effects, A.C.T.H. and/or cortisone should be withheld in the presence of thrombo-embolic complications.

Summary

An increased incidence of thrombo-embolic complications during A.C.T.H. and cortisone therapy was confirmed. During hormone therapy a higher dosage of ethyl biscoumacetate was needed to obtain plasma prothrombin activity at the optimum level.

Our grateful thanks are due to Dr. Mario Stefanini for his valuable help and suggestions.

References

Cosgriff, S. W. (1951). *J. Amer. med. Ass.*, **147**, 924.
—— Diefenbach, A. F., and Vogt, W. (1950). *Amer. J. Med.*, **9**, 752.
Dameshek, W., Saunders, R. H., and Zannos, L. (1950). *Bull. New Engl. med. Cent.*, **12**, 11.
Fahey, J. L. (1951). *Proc. Soc. exp. Biol., N.Y.*, **77**, 491.
Koller, F., and Zollikofer, H. (1950). *Experientia*, **6**, 299.
McGraw, A. B., Margulis, R. R., and Brush, B. E. (1952). *Arch. Surg., Chicago*, **65**, 81.
Quick, A. J. (1942). *The Haemorrhagic Diseases and the Physiology of Haemostasis*. Thomas, Springfield, Ill.
—— (1945). *Amer. J. clin. Path.*, **15**, 560.
Rosenthal, M. C., Saunders, R. H., Schwartz, L. I., Zannos, L., Santiago, E. P., and Dameshek, W. (1951). *Blood*, **6**, 804.
Smith, R. W., Margulis, R. R., Brennan, M. J., and Monto, R. W. (1950). *Science*, **112**, 295.
Stefanini, M. (1950). *Amer. J. clin. Path.*, **20**, 233.

A CASE OF UVEITIS WITH DEAFNESS

THE VOGT–KOYANAGI SYNDROME

BY

P. K. ROBINSON, M.B., M.R.C.P.

(Assistant Registrar, the National Hospital, Queen Square, London, W.C.1)

Uveitis may be caused by many disease processes, but it was Vogt (1906) who first described a case of non-traumatic uveitis associated with alopecia and greying of the eyelashes and hair. Koyanagi (1929) reviewed the published reports of ten such cases and added six of his own. In his review he summarized a hitherto ill-defined syndrome of uveitis, deafness, alopecia, and loss of pigment in the skin and the hair of the scalp, eyebrows, and eyelashes, which has since been named after these two workers. There is a closely related disease, named after Harada, in which a low-grade uveitis is associated with bilateral detachment of the retina, deafness, alopecia, and pigmentary changes similar to those already described.

The following case of the Vogt–Koyanagi syndrome is described in order to stimulate interest in the early recognition of such cases, so that investigations of the cause may be carried out at an early stage in the disease and perhaps a more specific method of treatment found.

Clinical Picture

A stoker aged 41 was admitted to the National Hospital under the care of Dr. M. J. McArdle on April 9, 1952. There was no significant family history. Apart from a urethritis of uncertain cause seven years before, he had been in good health.

Three months before admission he noticed swelling of a left inguinal lymph node without apparent cause. Soon after this he developed "a chill" with supraorbital headache and blood-streaked sputum on one occasion. Intermittent headache persisted for three weeks, during which time he noticed the insidious onset of misty vision, beginning in the right eye. Headache cleared spontaneously after a month, but vision slowly deteriorated. A month before admission he began to vomit, had right-sided tinnitus, and noticed difficulty in balancing. Two weeks later he became deaf on the right side, and a week afterwards deaf on the left also, by which time he had continual bilateral tinnitus.

On examination he was afebrile, but looked ill. His vision was R. 6/60, L. 2/60. Mr. Williamson Noble reported a bilateral granulomatous iridocyclitis with keratic precipitates and increase in ocular tension, particularly of the right eye. Haziness of the cornea prevented an adequate view of either fundus. Anosmia was not present. He was completely deaf in the right ear and could only just hear a loud voice with the left. There was no spontaneous nystagmus, although such had been observed just before admission. Caloric responses were absent (Miss Dix). The remaining cranial nerves were normal. There was no weakness, ataxia, sensory loss, or reflex abnormality in limbs or trunk, but the labyrinthine defects caused considerable dysequilibrium. There was no lymphadenopathy, and the chest and abdomen were normal.

Investigations.—C.S.F., April 10, 1952; pressure, 180 mm.; normal dynamics; 47 cells per c.mm. (93% lymphocytes, 7% monocytes); protein, 85 mg. per 100 ml.; Lange curve, 0112210000; W.R. (blood and C.S.F.) negative. April 23: pressure, 180 mm.; 34 lymphocytes per c.mm.; protein, 75 mg. per 100 ml.; glucose, 74 mg. per 100 ml.; chloride, 740 mg. per 100 ml.; no acid-fast bacilli seen; Löwenstein–Jensen culture and guinea-pig inoculation negative. May 17: pressure, 145 mm.; 18 cells per c.mm.; protein, 50 mg. per 100 ml.; Lange, no change. Full blood count, E.S.R. and serum protein were normal. Mantoux test was positive at 1 in 10,000. Blood agglutination test for brucellosis and dye and complement-fixation tests for toxoplasmosis were negative. *X*-ray examination of the skull, chest, hands, and feet (Dr. Davies and Dr. Thomson) revealed nothing abnormal. Urine: very faint trace of albumin; no sugar; centrifuged deposit contained a few leucocytes and red blood cells, but no casts.

Atropine drops were instilled into the eyes three times a day. In the next two days vision had deteriorated because of increased opacity of the media and raised ocular tension, but it subsequently began to improve. Although the cause of his meningeal reaction was uncertain he was given a course of penicillin (10 million units). Two weeks after admission he had complete and bilateral loss of cochlear and vestibular functions. Vision was R. 6/18 and L. 6/24. Progress was slow, and, since it was thought that the cause of his disease might be viral, a course of aureomycin (13.5 g.) was given. Mr. Keith Lyle saw the patient a month after admission and observed numerous posterior synechiae, pigment on the anterior lens capsule, turbid anterior chambers, keratic precipitates, and corneal oedema. Hyoscine ¼% eyedrops were used, afterwards changed to lachesine 1%. Two days later, and about six weeks after admission, he was discharged home. Visual acuity was 6/24 in each eye, but he was deaf in both ears.

One month later his visual acuity was R. 4/60 and L. 6/24. He was admitted to King's College Hospital, under the care of Mr. Keith Lyle, on June 16, 1952. He had a severe bilateral iridocyclitis with raised tension in both eyes, and visual acuity was 6/24 in both eyes. He remained bilaterally deaf. No alopecia, poliosis, or vitiligo was observed on admission, but a few scattered hairs over the temples and some eyelashes turned white later. Diagnostic lumbar and anterior chamber punctures were made and the fluids examined at the Institute of Ophthalmology. No virus was detected. He was treated with cortisone drops and subconjunctival injections and atropine. Visual acuity fluctuated and a paracentesis of the right anterior chamber

had to be performed on July 30 to relieve ocular tension. This rose again some months later and he was readmitted for a right paracentesis on February 13, 1953; but raised ocular tension persisted, and required a right broad iridectomy *ab externo* for its relief in March. In May Mr. Keith Lyle performed a similar operation on the left eye for a similar persistently raised tension. The post-operative course was uneventful. Visual acuity was R. 6/18 and L. 6/9 unaided. At the time of writing both eyes were white and free from congestion. There has been no further return of cochlear or vestibular functions, and no alopecia or vitiligo has developed.

Discussion

Investigations of the above case excluded syphilis, tuberculosis, sarcoidosis, brucellosis, and toxoplasmosis as the cause of the symptoms and signs, and, although neither vitiligo nor alopecia was observed, this does not preclude the diagnosis of the Vogt–Koyanagi syndrome. In analysing 47 recorded cases Rosen (1945) found greying of the hair (poliosis) in 90%, alopecia in 73%, vitiligo in 63%, and deafness in 54%. The aetiology of the condition remains unknown, although the association of ocular disease with pigmentary changes and disturbance of hearing has long been recognized. Both Nettleship (1884) and Hutchinson (1892–3) described cases of spontaneous iridocyclitis associated with poliosis, but Vogt's (1906) case also presented alopecia, and it was Koyanagi's (1929) review which led to the recognition of the syndrome under discussion.

A similar disorder, known as Harada's disease, has been recognized since Salus (1932) referred to Harada's original description of a low-grade uveitis with bilateral detachment of the retina, and to the observations of other Japanese workers that such a syndrome may be associated with deafness, alopecia, and poliosis. Givner (1943) and others have since recorded similar cases, in some of which vitiligo has also been noticed. The similarity between the Vogt–Koyanagi syndrome and sympathetic ophthalmia has been commented upon by Parker (1931), Carrasquillo (1942), and Hague (1944), and the latter condition has been recorded with whitening of the eyelashes (Schenkl, 1873) and deafness (Snellen, 1881). In addition to the clinical similarities mentioned above, a meningeal reaction has been recorded in the Vogt–Koyanagi syndrome (Hague, 1944; Jaffé, 1950), Harada's disease (Walsh, 1947; Cowper, 1951), and sympathetic ophthalmia (Corcelle, 1947).

The precise aetiology of these disorders is uncertain at present, although there is sufficient likeness in their clinical appearances to suggest they have a similar cause. Allergy and infection have been suggested as the causes of sympathetic ophthalmia, although the factor of trauma is also present here. Woods (1936) considered allergy to be the predisposing factor in this disease, and Duke-Elder (1940) stated that the cause is almost certainly infective (probably an unknown virus inhabiting the conjunctival sac), allergic sensitization to uveal pigment being responsible for the condition in the non-injured eye. In his review of the aetiology of the Vogt–Koyanagi syndrome Jaffé (1950) refers to the concepts of allergy, virus infection, and endocrine disturbance, but the evidence for endocrine dysfunction in such cases suggests that it is fortuitous rather than causative, and sensitivity to uveal pigment in patients suffering from the Vogt–Koyanagi syndrome has been variable (Rones, 1932; Carrasquillo, 1942). Hague (1944) attempted to correlate a virus aetiology with an endocrine disturbance by postulating that the clinical picture could be produced by a discrete infective lesion in the hypothalamus, but this somewhat ingenious suggestion does not bear critical examination, and Cowper (1951) believes that there is a widespread involvement of the nervous system in the Vogt–Koyanagi syndrome, and that this condition and Harada's disease represent different aspects of a basic uveoencephalitis.

The experimental work carried out on these non-traumatic syndromes suggests there may be an infective cause (Malbran and Muhlmann, 1936; Rados, 1940), and Friedenwald and McKee (1938) reported a case of endophthalmitis with a meningeal reaction, which they believed was almost certainly due to a virus, although they thought absolute proof was lacking because the virus isolated may have been native to the animals used in investigation.

Although there may be objections to the conclusions to be drawn from animal experiments in these two disorders of non-traumatic uveitis, there is more evidence in favour of a virus aetiology than anything else. The evidence at present available suggests that in these conditions and in sympathetic ophthalmia the most important factor is a virus infection, that allergy plays a part in the pigmentary disturbances, and that the various ocular manifestations depend upon the site of reaction in the uveal tract. Further progress can be made only by full and careful investigation in the early stages of the disease. The present case was not recognized as a case of the Vogt–Koyanagi syndrome before antibiotics were administered, and the negative viral investigations cannot therefore be taken as evidence against this mode of infection.

Treatment has, as yet, been of little avail in arresting the underlying disease process. There is a natural tendency towards spontaneous and good recovery of sight in Harada's disease, but in a group of 47 patients suffering from the Vogt–Koyanagi syndrome Rosen (1945) found that 30 had vision of 3/200 or less in each eye and only 7 had vision better than 20/50 in only one eye. Although deafness tends to disappear in most cases, in the one reported by Carrasquillo (1942) the auditory symptoms persisted, and this has been so in the case reported here. The syndrome therefore has a considerable morbidity. The present case is reported in order to stimulate interest in the condition and to encourage fuller use of future clinical material immediately it arises, particularly as the patients may be referred to an ophthalmologist, an otologist, a neurologist, or a general physician.

Summary

A case of the Vogt–Koyanagi syndrome is described. The points of similarity between this disorder and sympathetic ophthalmia and Harada's disease are given. As the aetiology of the condition remains unknown the importance of early investigation of future cases is emphasized.

I wish to thank the members of the staff of the National Hospital, King's College Hospital, and the Institute of Ophthalmology who assisted in the clinical and laboratory examination of the patient. In particular I wish to express my gratitude to Dr. M. J. McArdle and Mr. T. Keith Lyle for permission to report the details of the case under their care and for their helpful criticism in the preparation of this paper.

References

Carrasquillo, H. F. (1942). *Arch. Ophthal., Chicago*, **28**, 385.
Corcelle, L. (1947). *Brit. J. Ophthal.*, **31**, 366.
Cowper, A. R. (1951). *Arch. Ophthal., Chicago*, **45**, 367.
Duke-Elder, W. S. (1940). *Textbook of Ophthalmology*, **3**, 2324. Kimpton, London.
Friedenwald, J. S., and McKee, C. M. (1938). *Amer. J. Ophthal.*, **21**, 723.
Givner, I. (1943). *Arch. Ophthal., Chicago*, **30**, 331.
Hague, E. B. (1944). Ibid., **31**, 520.
Hutchinson, J. (1892-3). *Arch. Surg., Lond.*, **4**, 357.
Jaffé, N. S. (1950). *Amer. J. Ophthal.*, **33**, 571.
Koyanagi, Y. (1929). *Klin. Mbl. Augenheilk.*, **82**, 194.
Malbran, J., and Muhlmann, V. (1936). Cited by Hague (1944).
Nettleship, E. (1884). *Trans. Ophthal. Soc. U.K.*, **4**, 83.
Parker, W. R. (1931). *Amer. J. Ophthal.*, **14**, 577.
Rados, A. (1940). *Arch. Ophthal., Chicago*, **23**, 534.
Rones, B. (1932). Ibid., **7**, 847.
Rosen, E. (1945). Ibid., **33**, 281.
Salus, R. (1932). *Klin. Mbl., Augenheilk.*, **89**, 84.
Schenkl, A. (1873). *Arch. Derm. Syph., Wien*, **5**, 137.
Snellen, H. (1881). *Trans. Int. M. Congr., London*, **3**, 31.
Vogt, A. (1906). *Klin. Mbl. Augenheilk.*, **44**, 228.
Walsh, F. B. (1947). *Clinical Neuro-ophthalmology*, p. 552. Williams and Wilkins, Co., Baltimore.
Woods, A. C. (1936). *N.Y. St. J. Med.*, **36**, 67.

Medical Memoranda

Liver Abscess and Polyarteritis Nodosa

A case presenting with a large liver abscess, and multiple infarcts due to polyarteritis nodosa, is worth recording.

Case Report

A man aged 71 presented in September, 1950, with a four-months history of gnawing pain in the right hypochondrium, lassitude, loss of weight (2 st.—12.7 kg.), pallor, anorexia, nausea, and vomiting. He had had dysentery in India in 1918, and subsequent irregularly repeated attacks of right-sided abdominal pain until 1940.

The patient was a sallow thin man, afebrile, weight 8 st. (50.8 kg.). A firm tender liver extended into the right iliac fossa. There were signs of right basal pleurisy. B.P. 175/95. Heart and C.N.S., N.A.D. Hb, 9.5 g.; R.B.C., 3,200,000. P.C.V., 30%; W.B.C., 12,000 (polys. 78%); E.S.R. (Westergren), 70 mm. first hour. Trace of proteinuria. Blood urea, 31 mg. per 100 ml.; cholesterol, 131 mg. per 100 ml.; total proteins, 8.2 g. % (albumin 2.8 g., globulin 5.4 g.); bilirubin, 0.4 mg. per 100 ml.; thymol turbidity, 4 units; colloidal gold, negative; alkaline phosphatase, 20 units. Casoni test, negative. Hydatid C.F.T., negative. Faeces: no ova, cysts, amoeba, or occult blood. Chest *x*-ray examination showed considerable elevation of the right hemidiaphragm.

Progress

Diagnostic liver puncture on December 22 revealed turbid brown fluid. After a course of emetine hydrochloride, 10 gr. (0.65 g.) i.m. in 10 days, 1,500 ml. of similar fluid was aspirated from the right lobe of the liver. The fluid was sterile on culture (aerobic and anaerobic) and contained fat globules, macrophages, and amorphous debris only. Subsequent *x*-ray examination of the abdomen showed a large abscess cavity with a fluid level. His general condition improved after a course of chloroquine sulphate (13.2 g. in divided dosage). Recurrence of pain, weakness, anorexia, and cough necessitated readmission in April, 1951. The liver remained enlarged and tender three fingerbreadths below the subcostal margin. Hb, 85%; E.S.R. (Westergren), 69 mm. first hour; blood urea, 56 mg. per 100 ml.; B.P. 180/120. Initial symptomatic improvement followed a further course of chloroquine (6.4 g. in 14 days), but he relapsed in May with severe prostrating attacks of pain, vomiting, and rigors. A cerebral episode developed in June with stupor, periodic respiration, papilloedema, headaches, and vomiting. B.P. varied between 225/150 and 190/120. E.E.G. was abnormal. C.S.F.: protein, 100 mg. per 100 ml.; cells, 24 lymphocytes per cubic mm. Presumptive diagnosis was cerebral amoebiasis; courses of emetine (9 gr.—0.58 g.—in nine days) and chloroquine (6.4 g. in 14 days) were followed by improvement clinically and in the C.S.F. findings.

Further enlargement of the liver, however, soon occurred. Prolonged attacks of pain, dyspnoea, pallor, and nausea developed. Attacks increased in severity and duration till pain became constant, with paroxysmal exacerbations. A further course of emetine, 6 gr. (0.4 g.), was given. Further attempts to locate pus were unsuccessful, and the patient died on June 30, 1951.

Pathological Findings

Heart.—Fibrinous pericarditis; weight, 430 g.; left ventricular hypertrophy.

Lungs.—Right lung extensively adherent to right hemidiaphragm.

Liver.—Weight 1,400 g. Two amoebic abscesses were present in the right lobe: one, 20 cm. in diameter, at the upper extremity, underlying and adherent to the diaphragm; the other, 5 cm. in diameter, at the inferior margin in the midline. The wall of the larger cavity was composed of dense collagen with a ragged lining of necrotic material. No amoebae or organisms were demonstrable. "Iron pigment" was absent, suggesting that an origin from a recently necrotic area of liver was unlikely. The liver appeared fatty. There were large haemorrhagic areas, mainly in the right lobe, sometimes surrounded by paler more solid areas. Other totally pale areas resembling infarcts were also present. The smaller haemorrhagic areas were circular, and appeared to be aneurysmal sacs.

Kidneys.—Weights, 120 and 138 g. Elastosis in the larger and fibrinoid necrosis in the smaller vessels.

Lungs.—No vascular change.

Spleen.—Weight, 130 g.; normal.

Epididymis.—Aneurysmal vessels seen in the right epididymis similar to those in the liver.

Suprarenals.—Vessels of the capsule showed the identical haemorrhagic change observed in the smaller hepatic vessels and in the epididymis.

Hepatic Arteries.—In the portal tracts throughout the liver the small hepatic arteries all had thick walls and occasionally showed hyaline or fibrinoid change. The laminae were reduced, but there was little periarterial inflammatory reaction. In the haemorrhagic areas the arteries were often entirely blocked by a concomitant-intrinsic hyperplasia and had given rise to large areas of hepatic necrosis. In other cases the necrotic arterial vessels had given way with aneurysmal dilatation.

Mesenteric Vessels.—These showed destruction of the medial coat of the arteries with aneurysm formation.

Comment

It is probable that this patient had a long-standing amoebic abscess and developed polyarteritis during treatment. Atypical cases of amoebic abscesses have been diagnosed by liver aspiration (Van Raalte, 1949). The presence of polyarteritis nodosa was not diagnosed during life. There were several indications to which we should have paid more attention. The presence of proteinuria and hypertension was not readily explained, and the liver-function tests were persistently abnormal, which, as Sodeman (1950) pointed out, is very unusual in amoebiasis of the liver.

Pass (1935) showed that infarcts of the liver occur in polyarteritis nodosa, frequently becoming converted into abscesses which are difficult to distinguish from amoebic or other abscesses. Some cases of periarteritis nodosa with hepatic infarcts run a course similar to this case, including pain in the liver and even collapse of the right lower lobe of the lung (Davson *et al.*, 1948, Cases 10 and 11).

Our patient's attacks of pain, with circulatory collapse and dyspnoea appearing during the final illness, had been believed to be due to the tracking of an amoebic abscess. They were due, however, to multiple infarction. The episode of drowsiness and headache was presumably hypertensive encephalopathy. There was no post-mortem evidence of amoebic encephalitis.

The polyarteritis may have been caused by hypersensitivity to one of the many drugs given. These included chloroquine, emetine, penicillin, chloramphenicol, "amytal," and aminophylline.

Ian C. Gilliland, M.D., M.R.C.P.,
Temporary Lecturer and Physician, Dept. of Medicine, Postgraduate Medical School of London.

Geoffrey C. Manning, M.B., B.Ch.,
Medical Registrar, Middlesex Hospital, London.

References

Davson, J., Ball, J., and Platt, R. (1948). *Quart. J. Med.*, **17**, 175.
Pass, I. J. (1935). *Amer. J. Path.*, **11**, 503.
Sodeman, W. A. (1950). *Amer. J. trop. Med.*, **30**, 141.
Van Raalte, H. G. S. (1949). Ibid., **29**, 881.

Recovery from Sterility after Mumps Orchitis

The following cases would appear to be unique both in recovery from azoospermia after mumps orchitis and also in that conception occurred in the presence of severe oligospermia.

Case 1

The patient, aged 34, was married on December 8, 1945, his wife being aged 35, and a daughter was born on September 18, 1946. He developed mumps in July, 1948, with bilateral orchitis, followed by azoospermia, which persisted for over a year, as recorded in four consecutive semen analyses. There was no loss of hair, change of voice, or alteration in weight or libido to indicate any other endocrine dysfunction.

On May 28, 1949, for the first time, 50,000 spermatozoa per ml. were present, but there was no motility. There were 27% abnormal types, but no pus cells were present. On October 23 hormone assay revealed urinary ketosteroids as 24.2 mg. per 24 hours and gonadotrophic hormone output exceeding 55 m.u. in the same time. These increased values indicated a primary testicular failure. By April, 1950, however, his wife was three months pregnant, but the semen analysis was reported at the previous density of 50,000 per ml., and for the first time there was 50% motility. Unfortunately, she aborted, the abortion being confirmed by the patient's doctor. This improvement in the sperm viability had occurred without any specific treatment.

In November, 1950, the semen analysis again revealed an azoospermia, and he was given a high dosage of vitamin B complex, zygotrophin and thyroid, 1 gr. (65 mg.) daily, for two months. The semen now began to show considerable variation in sperm density, ranging from 180,000 to fewer than 20,000 per ml., while the post-coital tests showed a persistent absence of sperm.

The patient's wife had an extensive cervical erosion, and on gas insufflation the tubes were occluded. Cervical culture revealed a coagulase-negative staphylococcus. It was thought that this was a post-abortal infection, which of itself might cause sterility. The cervix was therefore cauterized and she was given a five-day course of intramuscular procaine penicillin, 300,000 units daily, "sulphatriad" orally, and triple sulphacream intravaginally.

Further post-coital tests were not carried out owing to my prolonged illness, but the last semen analysis in July, 1951, revealed fewer than 20,000 spermatozoa per ml., almost all dead and abnormal, with many pus cells and much epithelial debris.

In January, 1951, the patient's wife did not menstruate, and semen analysis on February 1, 1952, revealed a volume of 2.5 ml., 1,360,000 spermatozoa per ml., and 50% motility after four hours, but on March 31, 1952, only an occasional spermatozoon was seen after a long search, and this was the case also at the time of the last analysis, on August 20, 1952.

The wife was delivered on October 4 of a healthy boy weighing 7 lb. 12 oz. (3.5 kg.).

The following is a record of the consecutive semen analyses in this case, and of the dates of conception :

July, 1948: Mumps orchitis.

February, 1949: Azoospermia; volume 2.5 ml.

March, 1949: Azoospermia.

April, 1949: Azoospermia.

May, 1949: Volume 3 ml., 50,000 per ml.; no motility; 27% abnormal forms.

January, 1950: Conception occurred.

April, 1950: 50,000 per ml.; 50% motility. Abortion at three months.

May, 1950: Volume 2.1 ml.: 47,000 per ml.; 50% motility after four hours; 31% abnormal forms.

November, 1950: Azoospermia.

March, 1951: 180,000 per ml.

July, 1951: 20,000 per ml.

December, 1951: Conception occurred.

February, 1952: Volume 2.5 ml., 1,360,000; 50% motility after four hours.

March, 1952: Almost azoospermia; only one sperm seen after long search.

August, 1952: Azoospermia.

October, 1952: Delivered of full-term child.

Comment

The wife showed the common type of sterility following abortion where there is cervical infection with a spastic tubal occlusion as a defence mechanism against ascending infection (Sandler, 1952). This was treated by cauterization of the cervix without anaesthesia and by the administration of sulphonamides and penicillin. As the staphylococcal infection was coagulase-negative it was probably more saprophytic than pathogenic. The absence of spermatozoa in the post-coital test could have been due as much to the non-receptivity of the mucus as to the poor quality of the sperm. Unfortunately, it was not feasible to do an invasion test against fertile semen at that time.

It is difficult to believe that any treatment of the husband was effective. The recovery was probably due to natural processes of regeneration from islands of normal germinal epithelium left behind after the orchitis; nor is it possible to say what the actual sperm density was when conception took place. It is significant that the percentage of abnormal forms when recorded was always within the usual limits, indicating that the few cells left were producing a normal range of spermatozoa.

In only one of twelve semen analyses in a period of two years was the density as high as 1,360,000 per ml., and in fact had ranged down to actual zero. The average for the total period of observation was 142,000 per ml., whilst the viability has remained fairly constant at 50% after four hours. Conception had therefore occurred at a lower density than the figure 1,360,000 per ml., and this confirms the findings of White and Barton (1951), Harvey and Jackson (1945), and Sandler (1952, 1953) that conceptions can occur with extremely low sperm densities.

The possibility of deception in such cases must always be borne in mind, but in this particular case I am satisfied, from my personal knowledge of both patients, that this did not occur.

Case 2

A man aged 32, who had two children, aged 5 and 3, complained on April 24, 1953, of a sublingual swelling which was rapidly followed by painful bilateral swelling of the submaxillary glands. There was no parotid swelling. Two days later he developed a bilateral orchitis which was very severe, the pain being intense. He became so toxic that he could not be nursed at home and was transferred to hospital, where the diagnosis of mumps was confirmed. He made a rapid recovery, and on June 9 a specimen of semen revealed one or two non-motile spermatozoa.

Unfortunately, this patient was not seen again until March 24, 1954, when his semen analysis was: volume 3.2 ml.; spermatozoa 4,250,000 per ml., 85% dead. Abnormal forms: amorphic head 13%, pinhead 1%, curled 2%, double tail, 2%; total 18%. Motility good, but many oscillating.

He was now in excellent health and very active. His wife was already pregnant, her last menstruation having been in February, 1954.

Bernard Sandler, M.D., D.M.R., D.R.C.O.G.,
Medical Officer, Infertility Clinic,
Manchester Victoria Memorial Jewish Hospital.

References

Harvey, C., and Jackson, M. H. (1945). *Lancet*, **2**, 99, 134.
Sandler, B. (1952). *J. Obstet. Gynaec. Brit. Emp.*, **59**, 202.
—— (1953). Ibid., **60**, 67.
White, M. M., and Barton, M. (1951). *British Medical Journal*, **1**, 741.

Reviews

ST. MARY'S

The History of St. Mary's Hospital Medical School: A Century of Medical Education. By Zachary Cope. (Pp. 258; illustrated. 25s.) London: William Heinemann Ltd. 1954.

The teaching hospitals and medical schools of London have a proud and honourable history, the eldest of them, St. Bartholomew's Hospital, extending back to Norman times, while the youngest of all (except the Royal Free Hospital), St. Mary's Hospital, has reached its centenary this year.

This history, which, as its subtitle states, describes also a century of medical education, has been entrusted to the erudite and capable pen of Sir Zachary Cope. In increasing the reputation and teaching of the school, especially in surgery, he has played no small part. This is not apparent in the *History* itself, but some amends are made in the foreword by the Earl of Verulam, president of the medical school council, which pays a well-merited tribute to the author as a "loyal and devoted servant of the Hospital and of the Medical School."

The early chapters of the book describe the rise and passing of the private medical schools and the system of medical apprenticeship. Sir Zachary tells how the new hospital and medical school in Paddington were founded to meet the needs of a rapidly increasing population. The succeeding chapters describe the triumphs and progress of the school, which under the capable administration of its deans—here a special chapter is given to the successful work of Lord Moran—has done so much for modern medical education. Half the book is devoted to short, illustrated biographies of the staff of the school. To name but a few, what a galaxy they are: Burdon Sanderson, Broadbent, the three Lanes, Pepper, Spilsbury, Willcox, Waller, Leonard Rogers, Charles Singer, Almroth Wright, Fleming, and Leonard Colebrook. They have not only made their school illustrious, but their discoveries have benefited medicine and mankind. The book is admirably produced. While fulfilling its purpose as a history of St. Mary's Hospital and School, it is also a valuable contribution to the history of medicine.

Arthur S. MacNalty.

ISOTOPIC TRACERS

Isotopic Tracers: A Theoretical and Practical Manual for Biological Students and Research Workers. By G. E. Francis, W. Mulligan, and A. Wormall. Foreword by G. Hevesy. (Pp. 306; illustrated. 37s. 6d.) London: The Athlone Press. 1954.

When any important technique of investigation is increasing rapidly in scope and value there is need for a sound and simple description of its method for those who are starting to make use of it. The radioactive and stable isotopes have just such an extending field of application, and Professor Wormall and his colleagues have produced just the right book. They wisely avoid the temptation to enumerate the existing applications of tracer methods, for that has been done often and well already; they confine their account to those methods which depend on examination of samples rather than on counting *in vivo*, and have produced a supremely clear, sound, and readable description of what they are driven to call "isotope methodology." Their account deals in detail with the preparation and counting of samples for the main types of radioactive isotope, with mass spectrography, with the labelling of organic compounds, briefly with autoradiography, and adequately with the necessary precautions in the use of these materials. They then describe fully a dozen experimental exercises that they have included in the practical course on isotope techniques that has been running for the last few years at the Medical College of St. Bartholomew's Hospital.

The impression that this work gives is of the frankness and lucidity with which its authors describe the practical troubles as well as the principles of these methods, even to the best way of pouring liquid from an M6 counter tube. They might have dealt rather more fully with statistics of counting and given less on the symptoms of radiation sickness, which, as they say, should not arise in tracer work. They might perhaps have mentioned the possibility of radiochemical changes in labelled compounds kept on the shelf at high specific activity or of counts arising from potassium in reagents. They could have said more of scintillation counters, and particularly on the sensitivity of the "well" type. These, however, are details of emphasis which do not detract from the pleasure of reading a book which is so sound and clear on the field it covers.

E. Eric Pochin.

ANTITUBERCULOSIS VACCINATION

BCG and Vole Vaccination: A Practical Handbook. By K. Neville Irvine, M.A., D.M., B.Ch.(Oxon), M.R.C.S.(Eng.), L.R.C.P.(Lond.). Foreword by Frederick Heaf, M.A., M.D. F.R.C.P. (Pp. 96; illustrated. 12s. 6d.) London: National Association for the Prevention of Tuberculosis. 1954.

This is an excellent and authoritative short guide to the use of antituberculosis vaccines, by the author of *BCG Vaccination in Theory and Practice*. After summarizing the theory of vaccination and the properties of B.C.G. and vole vaccines he presents the main topics of the techniques of tuberculin testing and vaccination. A description of complications follows, and the book concludes with comments on organization specially directed to the British scene. The author has succeeded in compressing the essential information into a small space; the illustrations are good. He maintains a balanced view of the probable place of vaccination in public health work and stresses the difficulties of statistical appraisement; it might be added that the usefulness of the method is likely to differ with the varying epidemiology of the disease from country to country, and to change from one period to another. Chapter 6 might be better titled "Vaccination Techniques" instead of "Vaccination," and part of its introduction transferred elsewhere. "Lupoid reactions" should probably be changed to "lupus," since the conditions appear to be indistinguishable. It is implied that P.P.D. and O.T. are biologically equivalent, but there is recent evidence that the two are qualitatively different and that dose equivalence is not quite the same throughout the scale of potency; hence one should not change from the use of O.T. to P.P.D. without good reason. But these are minor comments on a most useful contribution, which can be recommended to all undertaking antituberculosis vaccination.

P. D'Arcy Hart.

SCIENTIFIC BASIS OF MEDICINE

Lectures on the Scientific Basis of Medicine. Volume II, 1952–3. (Pp. 380+xi; illustrated, with 29 plates. 35s.) London: The Athlone Press. 1954.

Some educators have toyed with the notion of two streams in our medical schools—the general practitioners and the specialists; others have discussed the possibility of a postgraduate diploma in clinical science or research methods. Neither of these ideas has got very far, for obvious practical reasons. In the meantime Sir Francis Fraser and his colleagues in the British Postgraduate Medical Federation have made an immense step forward in higher medical education by the series of lectures on "The Scientific Basis of Medicine," of which this is the second annual volume. The quality which distinguishes these lectures is that they deal with medicine as a science, whether it be Spence writing of planned clinical observation or Neuberger telling the story that leads from Garrod's observations on alkaptonuria to modern views on the relation between nucleic acids and protein synthesis. This science is not disinterested; indeed, the writers are fully aware of the possible implications of their work—as, for example, Wilson Smith writing about virus adaptability in relation to human disease; but it is

science and not technology, and it is this quality which distinguishes the series from other annual volumes on medicine and makes the lectures so stimulating to the researcher, the teacher, or the amateur of science.

Fraser states that each course of lectures is planned as a stage in an integrated, continuously developing survey, but it may prove even more important that they demonstrate that medicine is an active department of inductive science. One further point may be added. I had the experience this year of attending one of these lectures and finding the title had been changed to a subject to which I should not ordinarily have listened. The experience was informative and showed me how much we lose by restricting our research interests. In the light of this experience, and as a result of preparing this review, these lectures on the scientific basis of medicine can be confidently recommended to all who are interested in the science of medicine.

L. J. Witts.

FLUID BALANCE

Fluid Balance in Surgical Practice. By L. P. Le Quesnè, M.A., B.M., B.Ch.(Oxon), F.R.C.S. (Pp. 130; illustrated. 17s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1954.

This is an essentially practical manual of the methods of dealing with the problems of electrolyte balance that occur in clinical surgery. The theoretical background is covered briefly but adequately, and is illustrated by some of Mr. Le Quesne's own contributions in this field, thus maintaining the form of his Moynihan Prize Essay for 1953. The normal response to operation, administration of fluids and electrolytes in uncomplicated cases, dehydration, potassium deficiency, renal failure, water intoxication, and salt overloading are dealt with in turn. Brief sections on nitrogen and calorie problems and fluid balance in children follow. A valuable feature throughout is the critical discussion of the more important of the relevant literature. The monograph ends with some technical considerations and illustrative abbreviated case reports. The author makes two most reasonable pleas for uniformity. The first concerns the universal use of milli-equivalents as the unit of measurement, and the second a widespread and often misleading nursing practice—"Apparently unalterable custom decrees that oral fluids, vomit and urine output are measured in ounces, whereas intravenous fluids and aspirates are measured in cubic centimetres." The diagrams of electrolyte balances show positive balances below the line—and not above as in the convention used, for example, by Moore and Ball. The routine administration of potassium is recommended in the basic post-operative intravenous intake after the first 24 hours.

This little book is straightforward and practical in its approach. It will be of great value and interest to all those concerned in the care of surgical patients.

J. N. Ward-McQuaid.

"DR. BRIGHTON"

Brighton: Old Ocean's Bauble. By Edmund W. Gilbert. (Pp. 275+xvi; illustrated. 25s.) London: Methuen and Co., Ltd. 1954.

Professor Gilbert's book admirably fulfils his avowed purpose. From the bare threads of an incredible array of fact and figures is woven a colourful and fascinating tapestry vividly depicting many and varied scenes in the development of the Queen of Watering Places from her birth till 1950.

In 1750 Dr. Russell, of Lewes, by his advocacy of seawater and fresh air as therapeutic agents, put Brighton, then a collection of fishing huts, on the map as a health resort. As a result of the skill and enthusiasm of Dr. Russell and his successors "Dr. Brighton's" reputation soon became firmly established. During this period Brighton's clientele was small and exclusive. Royal patronage brought many social advantages, but in these days, when a health-giving holiday or a period of convalescence is within the reach of all, Brighton's reputation still stands high. Professor Gilbert shows how jealous of this reputation the inhabitants and rulers of Brighton became, and how, especially in the last fifty years, they have been receptive of new ideas to improve its medical and social amenities. He points out that Brighton was the first town to introduce voluntary notification of tuberculosis and the first to have a hospital entirely devoted to tuberculosis, and was also a pioneer of many municipal activities.

Modern Brighton is fully alive to its responsibilities, and, although the bath-chairs may have disappeared from the streets and the Martha Gunns from the beach, its patrons may expect that while balneology has not been forgotten a host of other facilities have been added to enable them to benefit from the unrivalled climatic conditions which prevail. "The holiday industry is a delicate plant and is easily injured," says the author, but Brighton need fear no injury from this factual yet interesting account of its life story, in which I have found no mistakes and few omissions. This book can be recommended to all, and especially to those who propose to attend the Annual Meeting of the British Medical Association in 1956 at Brighton.

A. H. Hall.

DRUG ADDICTION

Narcotics and Narcotic Addiction. By David W. Maurer, Ph.D., and Victor H. Vogel, M.D. (Pp. 303; 7 figures. 54s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. Toronto: The Ryerson Press. 1954.

The remarkable recent increase in the literature on drug addiction is a reflection of the astonishing growth of the vice itself. Furthermore, the spread of addiction is largely among the juvenile population, especially in the U.S.A. The authors show that admission of addicts under the age of 21 years to a group of special hospitals rose from 22 in 1947 to 440 in 1950. In England this affliction is also spreading amongst the juveniles, chiefly of the lower classes, though not to a comparable degree.

The book gives a refreshingly objective account of the whole field of drug addiction, including a brief historical survey, details of drug preparation, and methods of drug-taking; identification of drugs by clinical and laboratory observation; treatment of addiction; legal attempts to control the habit; and even the argot of narcotic addicts. Such an all-embracing treatise forms a most valuable reference book for those whose interest lies in this field, as also for the physician who may be faced unexpectedly with a drug addict.

One cannot study this subject for long without realizing how ineffective organized attempts at suppression of drug traffic have been. The world is far worse off in this respect than it was 50 years ago, when opium-smoking was a "gentleman's vice" and juvenile addiction in Europe and America was a rarity. A return to Victorian principles in the upbringing of children would do more to diminish this social evil than the Federal Narcotic Laws and the D.D.A. combined.

A. H. Douthwaite.

FOR DISSECTORS

A Handbook for Dissectors. By J. C. Boileau Grant and H. A. Cates. 4th edition. (Pp. 425+xiv; 26 illustrations. 27s. 6d.) London: Baillière, Tindall and Cox, Ltd. 1953.

This handbook was written as a dissection guide for use by students who are using as a textbook *A Method of Anatomy* by the senior author and therefore makes no pretence to being a textbook. Instructions given for the display of the structures of the body are concise, accurate, and readily followed. The few illustrations in the book are very schematic; nevertheless they serve the purpose for which they were designed. The absence of any general illustrations makes the book of less value than it otherwise would have been, except to those students using *A Method of Anatomy*.

W. J. Hamilton.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 2 1954

DISSEMINATED LUPUS ERYTHEMATOSUS

Disseminated lupus erythematosus is an unsatisfactory name for a disease that until recently was considered a rarity. The name is inappropriate because only a proportion of cases have skin lesions either at the onset or during the course of the illness, and the dermatological nosology is apt to detract attention from the fact that the condition is a generalized systemic disorder of collagen. The disease is now being diagnosed more often: during a four-year period Gold and Gowing,[1] in London, were able to study 26 cases, and in California 44 new cases were admitted to a general hospital during 1950 and 1951 (in the same period there were 18 cases of Hodgkin's disease and 39 cases of leukaemia—diseases not considered rare).[2] This raises a common problem: Is the disease on the increase or has it been misdiagnosed in the past? No satisfactory statistical answer is available, but certainly clinical awareness of the condition is now more acute, and by the use of new pathological techniques the diagnosis more readily confirmed.

The disease usually occurs between the ages of 20 and 40, and 80–95% of the patients are women. The reason for this sex preponderance is unknown, but it is of diagnostic importance. Often the first symptom is arthralgia, and the joint lesions may be indistinguishable from those in rheumatoid arthritis or acute rheumatic fever. Later other serous membranes are affected, and pleurisy (with or without effusion), pericarditis, or abdominal pain (due to peritoneal involvement) may be added. Raynaud's changes in the digits occur in about a quarter of the cases. Fever is a constant accompaniment, and the disease may present as a pyrexia of undetermined origin. Lymph-node enlargement and hepatomegaly occur in about 25% of cases, splenomegaly less often.

Skin lesions are found in three-quarters of the cases seen in a general hospital.[2] Erythematous patches, often impalpable and varying from pink through red to a livid cyanotic tint, are found characteristically over the cheeks and bridge of the nose (the typical butterfly rash) and on the V-shaped area of the neck and chest. Many patients with chronic discoid lupus erythematosus never manifest any symptoms of systemic disease, while others develop the disseminated condition which may be precipitated by a variety of drugs and physical agents, especially exposure to sun. Gold and Gowing,[1] with their extensive dermatological experience, believe that the chronic discoid form of lupus erythematosus may merge imperceptibly with the generalized disseminated form. "The more carefully patients with the discoid disease are investigated the more often does systemic involvement appear probable. . . ."

In the disseminated disease important, but not diagnostic, laboratory findings are leucopenia, a gradually developing anaemia, thrombocytopenia (which may be associated with purpura or haematuria), albumin and red cells in the urine, increased plasma globulin concentration, a high sedimentation rate, and a false positive Wassermann reaction.

The most significant and probably pathognomonic finding is the detection of the so-called lupus erythematosus cells (L.E. cells),[3] obtained from venous blood or bone-marrow aspirate. The L.E. cell is a neutrophilic polymorphonuclear leucocyte containing a purple-staining, smoky, homogeneous mass of material which pushes the nucleus to one side of the cell. The purple-staining material is largely desoxyribonucleic acid derived from enzymic disintegration of nuclear material and ingested by the leucocytes. Hamburger[4] has found that the addition of plasma from a patient with disseminated lupus erythematosus to heparinized normal bone-marrow will also produce L.E. cells. The factor responsible for inducing the change is heat-labile and resides in the gamma-globulin fraction of the plasma proteins.[5 6] Whatever may be the mechanism of the L.E. cell phenomenon, its demonstration has proved invaluable in diagnosis. A positive reaction is found in about three-quarters of all cases, and more frequently when there is hyperglobulinaemia greater than 3.8 g. per 100 ml. Repeated examinations may be required to reveal the cells because the phenomenon fluctuates in degree from time to time. Although L.E. cells have been reported in other conditions with hyperglobulinaemia (myelomatosis, hepatic cirrhosis, and leukaemia) the phenomenon is almost pathognomonic of disseminated lupus erythematosus.[7]

The course of the disease is very variable. Sometimes death from infection, toxaemia, or renal failure occurs within a few weeks. In other patients the course is subacute or chronic, with exacerbations and

[1] *Quart. J. Med.*, 1953, **22**, 457.
[2] Dubois, E. L., *Calif. Med.*, 1954, **80**, 154.
[3] Hargraves, M. M., *et al.*, *Proc. Mayo Clin.*, 1948, **23**, 25.
[4] *Yale J. Biol. Med.*, 1950, **22**, 407.
[5] Haserick, J. R., *Arch. Derm. Syph.* (*Chicago*), 1950, **61**, 889.
[6] —— and Lewis, L. A., *Blood*, 1950, **5**, 718.
[7] Dubois, E. L., *Arch. intern. Med.*, 1953, **92**, 168.
[8] *Lancet*, 1951, **2**, 755.
[9] Wells, G. C., *J. invest. Derm.*, 1952, **19**, 405.
[10] Pillsbury, D. M., and Jacobson, C., *J. Amer. med. Ass.*, 1954, **154**, 1330.
[11] Dubois, E. L., *et al.*, ibid., 1952, **149**, 995.
[12] Perry, Jr., H. M., and Schroeder, H. A., ibid., 1954, **154**, 670.
[13] Reinhardt, D. J., and Waldron, J. M., ibid., 1954, **155**, 1491.
[14] Shackman, N. H., *et al.*, ibid., 1954, **155**, 1492.

remissions of many months' duration. Evidence of renal involvement usually implies a bad prognosis.

At necropsy there is often a paucity of characteristic gross anatomical changes, but in a few cases the lesions originally described by Libman and Sachs—"non-bacterial valvular and mural atypical endocarditis"—are found in the heart. Usually, however, the changes resulting from intercurrent infection dominate the picture or there are non-specific changes of pleuritis or pericarditis. Microscopically the small arteries and arterioles of various viscera, especially the kidneys, may show fibrinoid degeneration and necrosis, with proliferation of the lining endothelium and thrombotic occlusion. Characteristically the walls of scattered glomerular capillaries are grossly thickened and hyalinized, and stain strongly with eosin (the wire loop lesion); the adventitia of the penicillary arteries of the spleen are surrounded by concentric rings of connective tissue (onion-skin lesions). In addition to the changes described as visceral angiitis, there may be widespread degeneration of connective tissue, which may contain free "haematoxylin bodies"—probably derived from nucleoprotein degeneration and the same material as is found in the L.E. cells.

No specific treatment for disseminated lupus erythematosus has been discovered. The observation of Page[8] that mepacrine is of value in the treatment of chronic discoid lupus has been confirmed,[9] and other antimalarial compounds, such as chloroquine,[10] are effective, probably by altering light sensitivity. These compounds do not influence disseminated lupus erythematosus, and the most helpful form of treatment is A.C.T.H. or cortisone,[11] particularly when given early before there is renal involvement. At page 777 of the *Journal* this week Dr. D. G. Richards describes three cases of disseminated lupus erythematosus, one with additional features of scleroderma. All were female, and equally characteristic were their symptoms and signs. Although hormonal treatment appears to have been life-saving during the acute episodes, it only suppresses the condition: it does not seem to alter the underlying disorder and may only tide the patient over until a spontaneous remission occurs. Recently there have been reports[12-14] of a collagen disease closely resembling disseminated lupus erythematosus, with L.E. cells present in several cases, affecting patients treated with hydralazine ("apresoline")—a substance used in the treatment of hypertension which has a strong affinity for certain heavy metal ions and combines with carbonyl and sulphhydryl groups. Thus it may prove possible to produce the disease in experimental animals at will and study its pathology more closely.

DOCTORS' SURGERIES

In his field survey of general practice in 1951–2, Dr. Stephen Hadfield[1] found, in his opinion, 10% of practice premises to be unsuitable. Dr. Stephen Taylor[2] in his later survey remarked upon the negative, taken-for-granted attitude of both doctors and patients to some of the bad surgeries he saw. The more recent report[3] of the Central Health Services Council's Committee on General Practice within the National Health Service (the Cohen Committee) is outspoken and says that "independent observers have been shocked by the low standards of accommodation and equipment provided by some doctors in some areas." All three reports recognize the many physical and financial difficulties which have conspired to aggravate the situation, but the Cohen Committee—a committee with official standing—clearly thinks that the time has come for action. It recommends that executive councils should make arrangements to ensure that surgery accommodation is adequate and lays down some general standards for their guidance. Recent Parliamentary questions are not the only evidence of consumer interest in this matter, for trades councils throughout the country are investigating conditions of doctors' surgeries and a report is to be prepared by the Federation of Trades Councils for the T.U.C.[4] Since, therefore, there is a feeling that all is not well, no one can feel content to leave the position as it is.

The profession itself has not been inactive. In October of last year the chairman of the Association's General Medical Services Committee wrote[5] on behalf of his committee to all general practitioners drawing attention to their responsibilities under their terms of service and earnestly hoping "that every general practitioner will do his utmost to provide the highest possible standard of surgery and waiting-room accommodation for his patients" in the belief that doctors would be "concerned to ensure that their practice premises are compatible with the prestige and status of general practice in the Service." Although there is no reason to doubt the observations that have been made about surgery accommodation, and there should be no complacency, nevertheless precise information is lacking about the magnitude of the problem. If there are bad surgeries, how many are there, and how bad? The General Medical Services Committee has now decided that the time has come when allegations must be answered, and that there should be a general survey of practice accommodation. We

[1] *British Medical Journal*, 1953, 2, 683.
[2] *Good General Practice*, 1954, Oxford University Press, London.
[3] Central Health Services Council. Report of the Committee on General Practice within the National Health Service, 1954, H.M.S.O., London.
[4] *Manchester Guardian*, September 22.
[5] *British Medical Journal Supplement*, 1953, 2, 165.

publish in this week's *Supplement* the first step towards this in the form of a letter from that committee to all local medical committees in England and Wales asking them to carry out inspections of surgery premises in their area and to report on the situation. The letter goes on to ask that when accommodation is found to be unsatisfactory the doctor should be advised to make improvements, and that the local committee should ensure that these are carried out within a reasonable time. This action has been taken with the agreement of the Minister of Health, who has written to executive councils asking them to co-operate with local medical committees where necessary.

The survey should give for the first time a true picture of surgery accommodation. It may substantiate or refute much of what has been said. Whichever way it is, the General Medical Services Committee has done well in grasping the nettle firmly and in keeping the initiative in the hands of the profession. The alternative to the present proposal is administrative action. This might well mean an overall application of some basic standards of measurement which could not possibly take into account individual problems with the same understanding as could experienced professional men and women themselves in general practice. The members of local medical committees will have to exercise restraint and tact, as well as spending time and trouble, in carrying out the survey, for some difficult problems may arise. But with a proper realization on all sides of the issues at stake there seems no reason why this combined operation to promote the good of general practice should not be successful.

MEIGS'S SYNDROME

In 1937 Meigs and Cass[1] reported that seven women with fibroma of the ovary associated with ascites and hydrothorax had been cured by simple removal of the tumour, and six years later Meigs and his colleagues[2] described a further score of such cases. Not surprisingly, therefore, this condition is now generally known as Meigs's syndrome, but the association of the various features had been noted many years before. In 1892 Lawson Tait[3] described a typical case and its cure by removal of the fibroma, and some ten years later Demons[4] wrote a full account of the syndrome. Yet it was Meigs who revived interest in this condition, and in a recent paper[5] he discusses the syndrome at length and gives in detail the features of 84 published cases. He insists that the name be restricted to cases in which the ovarian tumour is a benign fibroma, fluid is present in both peritoneal and pleural cavities, and the fluid disappears from both sacs and does not recur after the tumour has been removed. In particular, cases in which the ovarian neoplasm is cystic or malignant are excluded by definition.

This syndrome presents many fascinating features. The amount of fluid in abdomen and chest is not proportionate to the size of the tumour. The fluid is free from cells, except in the rare case when it is bloody, and it is sterile. Indeed, this type of pleural effusion is never accompanied by fever unless infection has been introduced at tapping. Drainage of the abdomen does not clear the fluid from the chest; it reaccumulates rapidly after thoracentesis, but disappears within three days to three weeks of the removal of the ovarian tumour. Regardless of the side of the fibroma, the fluid in the chest is on the right side alone in over 60% of cases, on the left side alone in about 10%, and bilateral in the remainder. But most speculation has centred on why there is fluid in the abdomen and how it reaches the pleural sac. Meigs reviews the various theories offered and the experimental work carried out. He himself speculates that the fluid escapes from the surface lymphatics of the fibroma, provided the latter is oedematous, for ascites accompanies only a minority of all cases of ovarian fibroma. He concludes that there must be some simple normal way of communication between the two cavities. The fluid may pass through the diaphragm either by way of lymphatics or possibly through the interstices between the cells of the diaphragm; but possibly the pleuroperitoneal sinus is the channel of transport, as suggested by Sweet.[6] Deacon[7] also entertains the possibility of communication by way of a congenital opening between the two cavities.

Meigs states that experimental work indicates that the passage of fluid is from abdomen to chest and not in the reverse direction. But that transport can occur in either direction has been neatly demonstrated by Cowan and his colleagues.[8] They studied the transport of radioactive colloidal gold (Au^{198}) between the pleural and peritoneal sacs in a woman with a mesenteric liposarcoma, ascites, and bilateral hydrothorax. By definition such a case of a primary malignant tumour is excluded from Meigs's syndrome, but this does not invalidate the findings. After abdominal paracentesis, 150 millicuries of Au^{198} were injected intraperitoneally. Within two hours the radioactive material was found present in the pleural fluid and in maximum concentration, and by 46½ hours 3.4% of the total dose injected was recovered by thoracentesis from the right pleural cavity. Eight weeks later the experiment was repeated in reverse, 56.8 millicuries of radioactive gold being injected into the right pleural sac. Within 40 hours 5.5% of the total dose was recovered by incomplete paracentesis of the peritoneal cavity. The concentration of gold in the ascitic fluid reached a maximum within one hour of intrapleural administration and thereafter decreased exponentially with time. Cowan and his associates consider that their studies in this case suggest that there is no direct communication between peritoneal and pleural sacs, and that the blood stream is not the

[1] *Amer. J. Obstet. Gynec.*, 1937, **33**, 249.
[2] Ibid., 1943, **46**, 19.
[3] *Med.-chir. Trans.*, 1892, **75**, 109, London.
[4] *Rev. mens. Gynéc. Obstet.*, 1903, **5**, 184, Bordeaux.
[5] *Amer. J. Obstet. Gynec.*, 1954, **67**, 962.
[6] *Thoracic Surgery*, 1950, Philadelphia.
[7] *British Medical Journal*, 1954, **1**, 317.
[8] *Surg. Gynec. Obstet.*, 1954, **98**, 721.

channel of transport. It seemed most likely to them therefore that some form of rapid transdiaphragmatic lymphatic transport was the explanation of their findings. This conclusion is that reached by most workers, but much further research is required before it can be considered fully established.

TREATMENT OF MEASLES ENCEPHALITIS

In general, the more numerous the methods of treatment of a given disease, the more doubtful the efficacy of any particular one. Measles encephalitis carries a mortality rate of 10%–40% and an incidence of nervous and mental sequelae of 30%–60%. Therapy has ranged between the use of, and the condemnation of, cerebral stimulants, the daily performance of lumbar puncture (with its danger in cerebral oedema), and intravenous hypertonic solutions and magnesium sulphate enemata (though dehydration has often failed). Gamma globulin has not prevented this complication, nor has convalescent-measles serum modified its course even when given intrathecally.

Assessment of therapeutic results is difficult owing to the uncertainty of ultimate prognosis even in deeply comatose cases. Thenebe[1] treated four such children with daily intravenous plasma (500 ml.), all recovering within 48 hours. Hamilton and Hanna,[2] studying 44 cases, gave symptomatic treatment to 18, with 10 recoveries and 5 deaths; convalescent sera to 10, with 5 recoveries and 5 deaths; and intravenous T.A.B. vaccine to 16, with 9 recoveries and only 1 death (2 others had sequelae and 4 were not traced). The authors felt that the results of the vaccine treatment were hopeful, and now from the same centre Knouf and Bower[3] report on 215 cases covering a twelve-year period. Of these cases, 152 recovered spontaneously concurrently with fall in pyrexia, 45 remained afebrile but comatose, and 5 were showing early responsiveness. These last 50 were given T.A.B. vaccine in initial dosage of 100,000,000 organisms, at first intravenously, later intramuscularly, and repeated daily, the dose being regulated to give a pyrexia slightly under 103° F. (39.4° C.). The vaccine was given in 300–500 ml. of 5% dextrose for intravenous use. Treatment was continued until the patients were both clinically and electroencephalographically normal—a result which was achieved in every case except one, and with no deaths. This is a startling claim, and it needs backing with a more detailed clinical account, in particular of the untreated cases, for these had a corrected death rate of 2.7%—itself very low, and indicating a high standard of general care. No mention is made of sequelae, and there was a high proportion of rapid complete spontaneous recoveries (152 cases). The authors do not discuss the rationale of this treatment, but protein shock has for long been given for hypersensitivity states and artificial pyrexia for demyelinating disease. If some abnormal antigen–antibody reaction exists, as in the experimental allergic encephalomyelitides, there may be some parallel, and one might expect some benefit from cortisone and A.C.T.H. Ligterink[4] and Shaw and Jack[5] do report favourably on their use, but Miller and Gibbons were disappointed with their experience.[6] Dr. W. F. T. McMath records in his account of ten cases of meningoencephalomyelitis at p. 789 of this week's *Journal* that A.C.T.H., given to two of them, failed to influence the course of the disease. The drug was given rather late, however, and the cases were severe.

There is no doubt that careful nursing must remain of supreme importance; comatose patients will require nasal feeding, with protein and vitamin supplements, and electrolyte balance must be maintained. Antibiotics are needed to prevent pulmonary infection, and a respirator should be available to treat the case of sudden, but often transient, respiratory failure. Physiotherapy is required long before the patient can co-operate. These recent reports show a refusal to accept the too prevalent attitude of despair towards treatment of neurological disease, and as such are encouraging.

[1] *Arch. Pediat.*, 1948, **65**, 302.
[2] *Amer. J. Dis. Child.*, 1941, **61**, 483.
[3] *Calif. Med.*, 1954, **81**, 18.
[4] *Ned. T. Geneesk.*, 1951, **95**, 3490.
[5] *J. Pediat.*, 1952, **40**, 383.
[6] *British Medical Journal*, 1953, **2**, 1345.

ACCIDENTAL CARBON MONOXIDE POISONING

The general public, and probably also the medical profession, may be both shocked and surprised to learn that the toll of life represented by accidental cases of coal-gas poisoning in England and Wales amounts to 400–500 cases annually. Relying comfortably on the convenience, speed, and comfort of modern appliances for providing gas for heating rooms and hot water, for cooking and refrigerators, the householder must find it hard to realize that a menace to health and life may be almost as readily established. Elsewhere in this issue Dr. Keith Simpson analyses the causes of death in 100 such cases and shows that most of them can be attributed to human defects in the shape of age, decrepitude, carelessness, and ignorance of the importance of adequate ventilation, while a small number reflect defects in the gas supply, such as fractured mains, leaky apparatus, and the use of the common meter with the almost inevitable risk of one consumer putting in coins without the knowledge of another. The answer to the problem provided by this smaller group of accidents is fairly obvious—continual and careful attention to the mechanical aspect of the main supply of gas and of the domestic appliances which place it within reach of the householder, some system of warning notice attached to every piece of apparatus supplied, and complete prohibition of the common meter. These are measures which can and should be taken by the suppliers of gas without delay.

Dealing with the human element is less simple. The elderly woman, living alone, whose trembling fingers fail to turn off the gas tap completely, the drunken man who blunders against a tap, the careless householder who allows vents to be blocked by dirt or objects such as birds' nests—these cannot be completely controlled by preventive measures, but the consequences of their carelessness or incapacity can be rendered less serious

by the provision of some device, such as a spring return to the "off" position of the tap. The suggestion has been made that in addition to these measures some substance should be added to gas at its source to render it more obnoxious and therefore more likely to give warning of its presence. The word "obnoxious" in this connexion implies that the constituent added must be either irritant or malodorous. There are objections to both alternatives, and the latter would of course be ineffective in any case in the small number of people who suffer from complete loss of sense of smell. These would no doubt be awakened from sleep or probably warned of danger by the sneezing caused by the presence of a fairly strong irritant, but the discomfort and disturbance caused to the normal person constantly using gas in the course of household or other duties make such an addition both inadvisable and impracticable. The second alternative, the addition of a substance with an unpleasant odour, has in fact been carried out in the U.S.A., the substance added being mercaptan. The objection in this country is a purely statutory one—the existence of an Act of Parliament passed in 1949 stating that "no area board shall supply gas containing carbon monoxide unless it possesses the distinctive pungent smell of coal gas." It is perhaps a debatable legal point whether the masking of this "distinctive pungent smell" by a substance with a different and more powerful odour is to be regarded as implying that the distinctive pungent smell no longer exists, but perhaps such hair-splitting is beside the point. If the presence of an unpleasant odour were found to be really efficacious in reducing the unnecessary toll of death from coal-gas poisoning, even the revocation of an Act of Parliament would not seem to raise an insuperable objection to such a life-saving measure. In the meantime, surely Dr. Keith Simpson's suggestions about the safety of appliances in installation, warning publicity, and much more frequent and universal inspection could and should be put into effect without delay.

DIAL C FOR CANCER

For many years past some local authorities and voluntary organizations have attempted, for the most part rather tentatively, to provide the general public with information about cancer and to make it easy for those who think they may have the disease to seek advice. Fear of being thought foolish, or of embarrassing examinations and mutilating operations, leads to much silent suffering, and the best way of breaking these fears down has yet to be found. Earlier this week the Hull City Council put into operation a remarkable scheme, which should appeal to those people who are too nervous or ignorant even to consult their own doctor. Hull is unique in being the only city in Britain which manages the local telephone service. Consequently telephone subscribers there obtain a service of wider scope than the G.P.O. provides elsewhere. For instance, during Parliamentary elections they can dial a number and hear the candidates' addresses without having to leave their houses. Not long ago the Marie Curie Memorial Foundation suggested to the Hull telephone manager that he might consider making a record about cancer for what is locally called the "Phonodiary." A script was submitted, and after consultation between the medical officer of health and the local medical committee certain amendments were made which were approved by the Foundation. The text of the record which is now played when anyone in Hull dials the appropriate Phonodiary number is printed in full on page 807. According to newspaper reports hundreds of people listened to the record on the first day the service was available. All those interested in this difficult field of health education will wish to hear the results of the Hull scheme.

IS MONGOLISM A METABOLIC ERROR?

Mongolism is a common disease affecting up to 3.4 per 1,000 newborn infants.[1] Its cause is still unknown. It affects all parts of the body, including the brain, skin, lips, mucous membranes, heart, and skeleton. Some elements at least of the disease process must be already in operation in the second month of foetal life, since the failure of the interventricular septum to close is a common feature, together with other anomalies of early intrauterine life. All cases of mongolism are mentally defective, and most are of imbecile level. Mongols belong to the minority of certified mental defectives in whom there is a demonstrable structural change in the brain and other organs to account for the defect. In this they resemble other cases of imbecility and idiocy.

Adequate histological investigations of the brain in mongolism have still not been done. The work of Meyer and Jones[2] revealed gliosis as a common but not essential feature. Crome[3] has shown that, among low-grade defectives, the brains of mongols are relatively well preserved, that they do not suffer from gross local defects but have a general moderate reduction in weight, affecting particularly the cerebellum and brain stem, and that those parts of the brain last to develop are poorly formed—namely, the frontal lobe and the superior temporal gyrus. Thus the defect in the brain reflects that in the body as a whole, characterized by Shuttleworth[4] in the term "unfinished child." Diffuse disorders of this description seem likely to be associated with a metabolic error. The less diffuse abnormalities of the brain, such as porencephaly, or areas of gliosis or atrophy, are more commonly due to local factors operating over a relatively short time—for example, birth trauma, anoxia, irradiation, and rhesus incompatibility. A number of metabolic abnormalities associated with mental deficiency are known. They include phenylketonuria, cretinism, and some of the "lipoid" diseases, such as gargoylism and Tay-Sachs disease. In these conditions there is a diffuse affection of the brain without gross microcephaly or disturbance of the general structure.

Consideration of the somatic lesions in mongolism leaves the aetiology obscure. Thus, the effect of maternal rubella in the early months of pregnancy is to produce heart lesions, cataract, and mental deficiency in some cases.[5] All of these changes can also occur in mongolism, though the cataracts are usually minute and differently distributed.[6] On the other hand, disturbances of lens development are associated with at least one of the known metabolic errors which produce mental defect—galactose intolerance.[7] The known errors

of metabolism are often familial and potentially inheritable. Phenylketonuria behaves according to rule in this respect. If then mongolism is due to a metabolic deficiency, to a simple enzyme lack, it must be different from other such conditions in this respect, since the occurrence of more than one mongol in a sibship is a rare event. On the other hand, a well-authenticated case has been described by Lelong *et al.*[8] in which a patient with mongolism had a child who was herself a mongol.

There is another condition fairly common in the field of mental defect which produces a characteristic physiognomy and general shape with typical skeletal deformities. This is gargoylism. Unrelated gargoyles look like brothers and sisters just as do mongols. Gargoylism affects all or most of the tissues, as mongolism does. It may now safely be classed as a metabolic defect, though the precise nature of the faulty linkage is still in dispute.

The general dwarfing and immaturity which characterize mongolism have led to the suggestion of an endocrine defect. An example of this incompleteness of development is the failure of formation of the frontal sinuses and similar anomalies of secondary facial growth.[9] No attempts at substitution therapy have been consistently successful. Benda[10] states, "The problems of pathology of the pituitary in mongolism suggest a chronic pituitary deficiency." These findings have not been confirmed by other workers to an extent which would make it possible to class mongolism, as Benda does, as a condition due to pituitary hypofunction. Kearns and Hutson[11] blame "lack of effective pituitary hormone" for failure of therapy. These workers report that in mongoloid infants, as distinct from cretins, tests with radioactive iodine for thyroid function give normal results, but fail to say how their ten patients were divided between these two groups. Barthel[12] states that mongolism is due to a combined deficiency of thymus, pineal, and pituitary, claiming good results from substitution therapy as a result of a very limited trial. Wickstrom[13] believes that in mongoloid infants the lungs have the capacity, as in the foetus, to absorb glucose in quantity from the blood stream.

In any metabolic disorder the liver is of special interest. Benda[10] in a series of 50 necropsies of mongoloid patients found gross fatty change in the liver in the majority, with fibrosis in a high proportion. He attributes these findings to endocrine disturbance and dismisses the role of tuberculosis. He fails to consider the part played by bronchopneumonia and other incidental infections which so often cause death in mongolism.[14] The same problem arises in assessing the work of Shapiro[15] on the "shift to the left" which he found in the leucocytes of mongoloid patients. Crome has found that fatty change is equally common in the livers of low-grade non-mongoloid mental defectives as in those of mongols. He has not, however, found fibrosis in the livers of mongoloid patients.

In view of the lack of precise data and the suggestive analogies with other metabolic disorders it is essential that the biochemistry and endocrinology of mongolism should be methodically explored. Such few studies as have been done have yielded mainly negative results, but now that new techniques are available older findings should be re-checked in large numbers of cases, with adequate controls.

[1] Beidleman, B., *Amer. J. ment. Defic.*, 1945, **50**, 35.
[2] *J. ment. Sci.*, 1939 **85**, 206.
[3] Publication pending.
[4] *British Medical Journal*, 1909, **2**, 661.
[5] Gregg, N. McA., *Trans. ophthal. Soc. Aust.*, 1941, **3**, 35.
[6] Lowe, R. F., *Brit. J. Ophthal.*, 1949, **33**, 131.
[7] Ellenburg, L. L., and Peterson, J. C., *Amer. Practit. (Philad.)*, 1951, **2**, 602.
[8] Lelong, M., *et al.*, *Arch. franc. Pédiat.*, 1949, **6**, 231.
[9] Spitzer, R., publication pending.
[10] *Mongolism and Cretinism*, 1947, London, p. 170.
[11] Kearns, J. E., and Hutson, W. F., *Quart. Bull. Northw. Univ. med. Sch.*, 1951, **25**, 270.
[12] *Psychiat. Neurol. u. Med. Psychol.*, 1952, **4**, 152.
[13] *Acta paediat. (Uppsala)*, 1948, **35**, *Supplement I*, 243.
[14] Kirman, B. H., *Amer. J. ment. Defic.*, 1950, **54**, 484.
[15] *J. ment. Sci.*, 1949, **95**, 689.

ONE HUNDRED YEARS OF A MEDICAL SCHOOL

The story of a medical school, like that of most teaching institutions, is the story of its teachers. St. Mary's Hospital Medical School, which is celebrating its centenary (see p. 808), can look back upon as brilliant a staff record as any school can boast. It glories, to begin with, in three outstanding achievements in research which emanated from Praed Street: the observations of Augustus D. Waller which laid the basis of electrocardiography, the introduction of typhoid vaccination by Sir Almroth Wright, and the discovery of penicillin by Sir Alexander Fleming. It is significant that nearly half the space in the commemorative volume, *The History of St. Mary's Hospital Medical School*, by Sir Zachary Cope, himself a member of the staff for 35 years, should be devoted to biographies (the book is reviewed at p. 796 in this issue).

In the roll of names one notes many repetitions, father and son and even grandson, and more than one instance of uncle and nephew. Such examples come to mind as William and John Broadbent, father and son, physicians to the hospital. The name of Handfield-Jones, which is that of the present senior surgeon, appears in three generations. Charles Handfield-Jones, who was one of the earliest physicians to show an interest in pathological histology, was one of the original staff of the hospital one hundred years ago. At one time the *British Medical Journal* had a close link with St. Mary's, for Ernest Hart, who was dean of the medical school there in the 'sixties, became, while still dean, a famous editor of the *Journal*.

The School is proposing to extend its buildings in commemoration of its centenary. At present it occupies two and a half sides of a square. To make it stand four-square in Paddington will cost something over £400,000. The centenary wing will give new and extended facilities for several departments. An appeal is being issued, and donors of large sums, whether individuals or institutions, may have a laboratory or a floor named after them in which perhaps some future Almroth Wright or Alexander Fleming may gain new triumphs.

We record with regret the death on September 27 of Dame Janet Campbell, formerly senior medical officer for maternity and child welfare, Ministry of Health, and chief woman medical adviser to the Board of Education.

THIRD INTERNATIONAL CONGRESS OF NUTRITION

AMSTERDAM, SEPTEMBER 13–17

[FROM A SPECIAL CORRESPONDENT]

The programme of the Third International Congress of Nutrition, held in Amsterdam from September 13 to 17, would have seemed strange five years ago when much of Europe had only just recovered from the undernutrition, and in some cases famine, of the war years. Perhaps it is a natural reaction that nutritional scientists should now be turning their attention to more sophisticated themes. Two of the chief topics of discussion at this congress were problems in the main of the civilized world. The first was overnutrition; the second was the effects of non-nutrient chemical substances in foods, whether added intentionally or unintentionally. In either case, the emphasis here was on processed and manufactured foodstuffs. Malnutrition, however, was not entirely neglected, since one day was given to papers on kwashiorkor and nutritional liver disease.

In a short report it is impossible to do justice to such a wide variety of subject-matter, ranging from clinical medicine to food technology. Mention can be made of only a few papers on the topics which are of most interest from a medical point of view.

Mechanics of Obesity

The high-light of the session on obesity was the analysis by Dr. J. MAYER (Harvard) of the results of many years of experimental work. He made two points, simple in themselves, but of great general importance: first, that we cannot hope to understand the causes of obesity until we know more about the normal control of appetite—that mysterious homoeostatic mechanism by which, over a period of weeks or months, food intake is adjusted to match energy output with astonishing accuracy. Mayer has put forward the so-called glucostatic theory, according to which the regulation of appetite depends on the rate of utilization of glucose by certain centres in the hypothalamus. A reduction in arteriovenous glucose difference is accompanied by feelings of hunger and by gastric contractions, regardless of the absolute level of blood sugar. This hypothesis is consistent with many clinical facts, such as the increased appetite that is present both in diabetes and in hypoglycaemic states; nevertheless, it must be developed in greater detail before it can be regarded as more than tentative.

Mayer's second point was that obesity is not an entity; like fever, it is a manifestation of disturbed energy metabolism, with many different causes. This is well illustrated experimentally: in rats and mice it is possible to produce obesity in three ways—by destruction of regulating centres in the hypothalamus, by injections of gold thioglucose, and by inbreeding a strain of hereditarily obese mice. Investigation with isotopes of the rates of fat formation and turnover show that these three forms of obesity are metabolically quite distinct. Naturally the laws of thermodynamics must be obeyed; neither a mouse nor a man can put on weight unless its energy intake exceeds its output. This result can, however, be brought about in various ways. The hereditarily obese mice have a normal food intake, but are very inert, whereas the hypothalamic rats and mice are very active, but have voracious appetites. This has its parallel in man; in an investigation of obese girls in Boston it was found that the food intake was less than in a control group, but the activity of the girls was very low; for instance, they spent four times as long watching television. Another much rarer group were fat in spite of being very active, because they had enormous appetites. These are probably completely distinct syndromes, yet statistically, and very often clinically, they would be classified under the single heading "overweight."

The concept of obesity implies that there is a normal or standard weight which has been exceeded, and, as Mr. A. L. BACHARACH (London) pointed out, we must not ignore individual variations. The words "normal standard," he said, suggested the idea of desirability or aim; this desirability might to a large extent be a matter of fashion.

Dr. D. A. W. EDWARDS (London) showed that a reliable estimate of the total amount of body fat can be obtained from measurements of the thickness of subcutaneous skin folds. These measurements are very readily made, and a more widespread use of the method would be valuable, provided that a standardized type of calliper were used. The most satisfactory design was described in detail. It seems that this instrument would be a useful adjunct in any consulting-room, perhaps more useful than a weighing machine.

The official title of this session was "Overnutrition and Disease." However, only passing reference was made to the effect of obesity on expectation of life, and its relation to other diseases. Dr. G. C. KENNEDY (Edinburgh) showed that the life of rats made obese by hypothalamic injury was shortened and kidney lesions developed, which he interpreted as evidence of premature senility. The clinicians, however, remained in the background, and none came forward with any studies on man comparable to Mayer's penetrating experimental analysis.

Current Views on Kwashiorkor

The next group of papers was concerned with kwashiorkor, and so took us to the other end of the nutritional scale. This disease has been discussed in detail at a number of recent meetings, notably at that of the Commission for Technical Co-operation in Africa South of the Sahara, held in the Gambia in 1952, and at a conference convened in 1953 by the New York Academy of Sciences. Therefore Professor J. F. BROCK (Capetown), in a very lucid introductory paper, confined himself to a review of recent advances in our knowledge of the syndrome. Much of the confusion about clinical definition and terminology has gradually been cleared away. Although some workers would not agree, the balance of opinion now holds that kwashiorkor results from a diet deficient in protein but relatively much less deficient in calories. Such a diet is unbalanced; a balanced and equal shortage of all nutrients leads to simple undernutrition and inanition. The clinical picture of kwashiorkor may be complicated by concomitant vitamin deficiencies, which vary from one country to another according to the nature of the staple foodstuff. Moreover, as Brock warned, it would be unwise to neglect the possibility that deficiency of trace elements, or of essential factors as yet unknown, may play some causal role. He himself has shown by means of balance studies that there is a depletion of body potassium which seems to be two or three times as great as the depletion of protein. This has obvious implications for treatment, and Brock claims that the sudden death which is a common feature of the disease can be avoided by giving potassium. He also stressed the value of antibiotics administered prophylactically.

Dr. V. N. PATWARDHAN (Coonoor) next reviewed the types of liver injury in man which may be caused by malnutrition. This is an increasingly complex subject, as more and more syndromes are described from different parts of the world. One of the first in which liver damage was thought to be of dietary origin was the so-called "biliary" cirrhosis of infants in Southern India. The latest addition to the list is venous occlusive disease (V.O.D.) of the liver, from Jamaica. These two syndromes resemble each other in many ways; Patwardhan, however, believes that they are quite distinct. Whereas V.O.D. is thought to be the result of a combined dietetic and toxic injury, infantile cirrhosis in his view has no relation to nutrition.

Other speakers dealt with the biochemical changes in kwashiorkor. Dr. L. N. WENT (Djakarta) made the important point that alterations in plasma protein levels and in albumin–globulin ratio are not specific, but may be found equally in dystrophy or marasmus. This is probably true also of the reduction in activity of enzymes such as cholinesterase. It has not been convincingly shown that any of the changes in blood chemistry that have been described are specific, nor do they give any clear indication of severity.

Perhaps for that reason some workers are turning their attention to changes in the tissues. Reddish discoloration of the hair is a prominent feature of kwashiorkor, and Dr. F. ROBAZZA (Brussels) has shown that this hair has a decreased cystine content, although admittedly only one sample was analysed. Dr. H. M. SINCLAIR (Oxford) pointed out that such results must be interpreted with caution, since the structure and the composition of the hair vary from root to tip. Dr. J. C. WATERLOW (Jamaica) has studied the composition of the liver in biopsy specimens from cases of kwashiorkor, and found that the liver may lose nearly half its total amount of protein and ribonucleic acid—a very severe depletion.

The Bifidus Factor

The concept of protein deficiency, like that of obesity, implies a standard—in this case that of sufficiency. If anyone thinks he knows how much protein is sufficient for human needs his confidence would be shaken by Dr. P. GYÖRGY (Philadelphia). György has repeatedly posed the question: "Why is it that good growth occurs on a diet of human milk, in which only 6% of the calories are supplied by protein, whereas with all other foodstuffs, if growth is to be satisfactory, there must be enough protein to supply about 14% of the calorie requirement?" This question has not yet been answered, but while trying to answer it György discovered the *Lactobacillus bifidus* factor, in an investigation which is now well known. The starting-point was the well-known fact that *Lactobacillus bifidus* is the predominant organism in the stools of breast-fed infants, but not in those fed on cows' milk. A study of the metabolic requirements of this organism revealed a variant which would not grow unless human milk was added to the synthetic culture medium. The responsible factor in the milk was found to be a nitrogen-containing polysaccharide, allied to the blood group polysaccharides and to heparin. Human milk and gastric mucosa are rich in this factor, but cows' milk contains very little of it. The nutritional significance of this factor is uncertain; it has no effect on the growth of animals, and was found to be present in normal amounts in the milk of malnourished Jamaican women. It may, however, be very important in preventing infection in the infant. Although it has no antibiotic properties, it has been shown to inhibit the growth of influenza virus cultured on eggs. Although the detailed chemistry of this factor presents difficulties, it was clear that György's work represents a fine example of the scientific method—the step-by-step process of observation, deduction, and experimental trial.

Personality Changes in Malnutrition

It is probable that the most important effects of a deficient diet are not the physical but the psychological, whether we look at it from the ethical or from the political point of view—whether we think of the human misery or of the unrest and low work output for which malnutrition is responsible. This field has been much neglected because of the extreme difficulty of obtaining factual data. Dr. J. BROZEK (Minneapolis) described some of the work that has been done in Dr. Ancel Keys's laboratory, including the famous "Minnesota Experiment," in which severe and prolonged caloric and protein deficiencies were produced in human volunteers. A subsequent experiment has been done in which vitamin B_1 was restricted. None of these deficiencies produced any change in intellectual function, but they all caused impairment of motor performance and profound changes in personality. The latter have been assessed by a series of tests with the formidable title "Minnesota multiphase personality inventory." The changes observed are entirely non-specific; as the man-in-the-street might put it: "Hunger makes men bloody-minded."

If work such as that described by Brozek is difficult in the laboratory it is even harder in the field. Nevertheless, a start has been made. The survey done for W.H.O. by Dr. J. C. Carothers on the "African Mind in Health and Disease" has been followed up by the application in Uganda of standardized psychometric tests to assess the mental changes which are so pronounced in kwashiorkor.

THIRD INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

STOCKHOLM, SEPTEMBER 15–18

[FROM A SPECIAL CORRESPONDENT]

The Third International Congress of Internal Medicine, held in the Concert Hall at Stockholm from September 15 to 18. was attended by some 700 doctors and their wives from all parts of the world. The scientific business was chiefly concerned with discussions on hypertension and the collagen diseases.

Role of the Carotid Sinus in Hypertension

The first paper was by Professor C. HEYMANS (Ghent), who in 1938 won a Nobel prize for his work on the carotid sinus. Heymans reviewed the haemostatic functions of the carotid sinus and depressor reflexes, and pointed out the importance of understanding the extent to which these stretch receptors are stimulated in hypertension. He and his colleagues had shown that their response is determined not only by the arterial pressure distending from within, but also by the state of contraction of the arterial wall. Thus the local application to the carotid sinus of drugs that cause contraction of arterial muscle, such as adrenaline and noradrenaline, results in reflex fall of arterial pressure, while the local application of relaxants such as papaverine causes a rise of pressure. Further, hypertension produced experimentally in the dog by "cellophane"-induced perinephritis could be abolished temporarily by applying noradrenaline locally to the carotid sinus. Heymans therefore suggested that some forms of hypertension in man might be due to local changes in the large arteries interfering with the stimulation of the aortic and carotid sinus baroreceptors.

This subject was pursued later by Dr. H. LAMPEN, who had introduced a local anaesthetic into the region of the carotid sinus and its nerves. He found that the consequent rise of pressure was of the same kind and degree in patients with hypertension as in normal subjects. He concluded from this that patients with chronic hypertension have normally functioning baroreceptors.

Influence of Heredity

Next came Professor G. W. PICKERING (London), who dealt with the role of the genetic factor in essential hypertension. Study of a sample of the general population had shown that arterial pressure tends to rise with age, but that it rises more in some subjects than in others. In each decade the variation seemed to be continuous, and the division between normal blood pressure and hypertension was purely artificial. Essential hypertension is not a discrete entity, according to Professor Pickering, but a term applied to that section of the population whose arterial pressure lies above an arbitrarily defined value and who have no obvious lesion to account for it.

Relatives of patients with essential hypertension tended to have higher blood pressures at all ages, but showed no greater rise of pressure with age than the relatives of those with lower pressures. Use of a method of scoring which adjusts for the effects of age and sex permitted a genetic analysis which had shown that, in the upper ranges at least, arterial pressure seems to be inherited as a graded characteristic, and that the size of the genetic factor is represented by a regression coefficient of about 0.2. This means that for every 10 mm. rise above the norm shown by one member of a family the other members will tend to show, on an

average, a 2 mm. rise. The inheritance of hypertension was probably multifactorial, Professor Pickering concluded, and the small size of the genetic factor suggested that environmental factors are at least as important.

Noise and Excitement: Kidneys and Adrenals

Professor E. Rothlin (Basle) followed with a paper on the production of hypertension in rats by disturbing noises. Laboratory rats (Glaxo) had been exposed to such noises for up to 12 months without any alteration of blood pressure. But Glaxo rats crossed with the wild Norway rat yielded a strain which developed hypertension after two months' exposure. Stopping the noise at four months was followed after 30 days by a slow decrease in blood pressure, which became normal after four months: subsequent exposure to the same noise produced a quicker rise. The rise of pressure could be prevented or reduced by subcutaneous injection of "hydergine" (0.2 to 0.3 mg./kg.). Paradoxically, 2% sodium chloride given as drinking water produced an acute and fatal fall of pressure in rats rendered hypertensive by noise. Moreover, when hypertension had been produced by saline injection, the blood pressure of the rats was reduced by exposing them to noise.

The role of the adrenal glands in renal and renoprival hypertension was discussed by Dr. J. M. Ledingham (London). He pointed out that hypertension produced in rats by either renal artery constriction or total nephrectomy can be prevented by excision of the adrenals.

Professor M. Rosenheim (London) showed that the kidney should not be overlooked in human subjects, since removal of a unilaterally diseased kidney might abolish hypertension even in the malignant phase. He had found that nephrectomy was more likely to yield a cure when the intravenous pyelogram gave some shadow on the affected side, and instanced one successful case in which the lower pole alone was the seat of pyelonephritis.

A particularly interesting communication was that of Dr. A. L. Mjasnikow, unfortunately given in Russian at such a speed that the translator could not keep pace. To him hypertension is chiefly due to a disturbance between the conditioned reflexes and inhibitions demonstrated by Pavlov. It is the result of acute prolonged fits of nervous excitement. Your correspondent was unable to record the detailed evidence for this view, which is not unlike that of Harold Wolff, but the speaker indicated that in Russia they had produced experimental hypertension in monkeys through conditioned reflexes.

Finally, Professor U. von Euler (Stockholm) described the results of estimating noradrenaline in the urine in essential hypertension. In 56% of cases the excretion was normal, in the remainder raised. Some of those with the highest excretions might be undetected cases of phaeochromocytoma; in the remainder it was not improbable that the increased excretion reflected increased activity of the sympathetic vasomotor nerves.

Treatment and Prognosis

A large number of papers were given on the treatment of hypertension. Dr. Canosa Lorenzo (Cuba) referred to results obtained with rauwolfia, veratrine, "apresoline," and hexamethonium. He had obtained more pronounced falls of pressure by using the drugs in combination than singly. He preferred to begin with rauwolfia because of its low toxicity and to add others if results are inadequate. Professor Robert Platt (Manchester) showed beautiful fundus photographs of the disappearance of the papilloedema and exudate of hypertensive neuroretinopathy in response to hexamethonium therapy.

Dr. E. Nyman (Stockholm) considered the complications and disadvantages of the modern drugs—interstitial pneumonia with hexamethonium; lupus erythematosus, including reversible globulin changes and L.E. cells in the blood, with apresoline; and the very variable effects of rauwolfia. He pointed out that dangerous complications might ensue in elderly subjects with severe vascular change if arterial pressure were reduced.

The last section on hypertension dealt with prognosis. Notable was Dr. P. Bechgaard's (Aarhus) paper describing a further ten-year follow-up of the 700 survivors of his original 1,000 cases previously followed for ten years. Sixty-three of those who have survived for twenty years are now aged 75 and over, and 25 are over 80 years. As he had noted before, the mortality of those who were obese was no greater than those who were not. At his previous follow-up ten years ago, 13 of the original 1,000 had entered the malignant phase. Since then no further cases have done so. He concludes that the malignant phase occurs in scarcely more than 1% of those with essential hypertension; that it nearly always declares itself soon; and that long-continued benign hypertension protects against the malignant phase.

Collagen Diseases

The discussion was opened by Professor Paul Klemperer (New York), who gave a scholarly review of the subject illustrated by beautiful histological specimens. While fibrinoid necrosis of connective tissue, particularly in the walls of blood vessels, is the most conspicuous lesion of these diseases, it was probable that this might arise in more than one way and present peculiar features in different diseases. Thus, in disseminated lupus smudges are seen in the haematoxylin-stained preparation, probably composed of desoxyribonucleic acid, and representing degraded nucleoprotein that is the specific lesion of disseminated lupus. Again, the fibrinoid material in scleroderma is more resistant to trypsin than is that of malignant hypertension. Professor Klemperer considers that the specific alteration in these diseases is not so much in the collagen as in the basic intracellular substances, which may be related to alterations in plasma constituents. In this sense he accepts the term collagen diseases as a brief descriptive term. Dr. W. S. C. Copeman (London) followed with an excellent account of the clinical features of the collagen diseases, largely drawn from his own experience,

Hench's Indications for A.C.T.H. and Cortisone

Then came Dr. P. S. Hench (Rochester, N.Y.) with a review of the role of cortisone and A.C.T.H. in treatment. He stressed the fact that these are hormones, and that no hormone except thyroxine acts for more than a few hours. He classified the indications for these hormones as follows: (*a*) *specific replacement* in primary adrenal insufficiency, adrenal apoplexy, hypopituitarism, post-operative adrenal insufficiency, after adrenalectomy, adrenogenital syndrome, and spontaneous *hypo*glycaemia; (*b*) as the *treatment of choice* in, for example, haemolytic anaemia, bronchial asthma, dermatitis medicamentosa, lupus erythematosus, pemphigus vulgaris, early periarteritis nodosa, and acute rheumatic polyarteritis and carditis; (*c*) as *satisfactory treatment* for certain cases of, for example, progressive rheumatoid arthritis, nephrosis, allergic dermatitis, and severe delirium tremens; (*d*) as a remedy *of limited value* in such conditions as severe insect or snake bites, leukaemia, pruritus ani or vulvae, and acute viral hepatitis. One of Hench's most revolutionary recommendations was the use of these hormones with antibiotics in severe infections where antibiotics alone have failed. Successfully treated by combined therapy had been peritonitis, meningitis, septicaemia, bacterial endocarditis, and tuberculous meningitis and peritonitis. For acute conditions the hormones should be given in therapeutically effective doses as soon as possible and tapered off when the acute phase is over. In chronic diseases they could be given by either interrupted or continuous administration, these schedules being interchangeable. The best results were achieved, he said, by selecting the schedule best suited to the individual case. By such methods symptoms had been controlled satisfactorily and indefinitely (for two to three years to date) in over 50% of hormonally treated rheumatoid patients.

In the discussion which followed Dr. G. ASBOE-HANSEN (Copenhagen) and Dr. D. A. LONG (London) developed Klemperer's ideas of a generalized change in the mesenchyme. The former discussed the morphological and chemical changes produced by cortisone and thyroxine in the mesenchyme and in the intercellular substance. The latter pointed out the numerous similarities between rheumatic fever and bacterial allergy as represented by the B.C.G.-infected guinea-pig, particularly in their response to cortisone, thyroxine, and diabetogenic and antidiabetogenic agents.

Publication of Proceedings

There were numerous papers which your correspondent was not privileged to hear. Among them one by Dr. R. LUFT, Professor H. OLIVECRONA, and Professor T. SJÖGREN (Stockholm) reported beneficial effects from hypophysectomy in Kimmelstiel–Wilson syndrome in diabetes mellitus. Those wishing for further information will find it in full in the Proceedings of the Congress to be published as a supplement to *Acta Medica Scandinavica*, and available if ordered in time from the secretary of the Congress at a price of 10 Swedish kronen (about 14s.).

MEDICAL DEFENCE UNION

The annual meeting of the Medical Defence Union was held at its offices in Tavistock House South, London, on September 21. Dr. S. COCHRANE SHANKS, in presenting the annual report, said that the membership for the first time in the history of the Union exceeded 40,000, an increase during the year of some 2,000. He welcomed two new vice-presidents in Dr. P. T. O'FARRELL, of Dublin, and Professor W. E. HERBERT, of Guy's Hospital Dental School.

Assisted Litigation

Dr. SHANKS went on to speak of the increasing burden of litigation. During the year 2,384 cases had been handled, compared with 2,266 in 1952. In about 80% of the cases brought against doctors the plaintiff was legally assisted under the Legal Aid Scheme. In two cases undertaken by the Union on behalf of members during the past year the hearings extended over 11 and 13 days respectively; one case proceeded to the Court of Appeal, and in both cases judgments were returned in favour of the members. The sums expended by the Union in defending these cases were about £7,700 and £2,600 respectively, none of which was recoverable from the plaintiffs, who were legally assisted persons. He thought that a case could be made out for imposing on a plaintiff some portion of the costs of a successful defendant. There was a feeling that the legal aid scheme operated unfairly, and here he quoted some remarks of Mr. Justice Stable: "I shall go on protesting against this system under which the State subsidizes litigants and then does not pay the costs of the other side when the assisted person loses."

The sums paid by hospital authorities in England and Wales in compensation, mostly as damages for alleged negligent treatment, had been published recently by the Minister of Health. In 1950 the sum was £23,000, in 1951 £38,000, in 1952 £106,000, and in 1953 £153,000. Judges if not juries were beginning to realize that mishaps could occur in treatment when there was no suspicion of negligence. Lord Justice Denning had thus put the matter in a recent judgment: "Every surgical operation involves risks. It would be wrong, and indeed bad law, to say that simply because a misadventure or mishap occurred, thereby the hospital and doctors are liable. Indeed, it would be disastrous to the community if it were so. It would mean that a doctor examining a patient, or a surgeon operating at a table, instead of getting on with his work, would for ever be looking over his shoulder to see if someone was coming up with a dagger. For an action for negligence against a doctor is for him like unto a dagger."

Perhaps the most important event of the year, Dr. Shanks continued, had been the conclusion of an agreement between the British Medical Association, the defence societies, and the Minister of Health relating to actions for damages against hospitals and doctors. As a result of this agreement the Ministry had withdrawn its previous instruction to hospitals to join doctors as co-defendants or seek contributions from them after the event. This would obviate the spectacle of doctor and hospital authority fighting each other in the courts. Whether this agreement with the Ministry would involve the defence society in greater expense or not it was impossible to say, but the defence society would not have to pay more than its just liability, and would gain by the restoration of good will between hospital and doctor. The good will existed before the Act, but since 1948 it had been declining. He was happy to think that the Union had played a large part in the negotiations which had led to this agreement. Dr. Shanks concluded with a tribute to the Union staff, headed by the secretary, Dr. ROBERT FORBES.

Dr. JANET AITKEN and Mr. ST. J. D. BUXTON, who retired by rotation, were re-elected members of council, and Dr. F. B. WINFIELD was elected a new member. The vice-presidents, of whom there are seventeen, were also re-elected.

CANCER EDUCATION BY TELEPHONE

THE HULL EXPERIMENT

Below is printed the script of the record on cancer which any member of the public in Hull can have played to him over the city's telephone system. The fact that the telephone system belongs to the city and not to the General Post Office makes this possible. This new departure in cancer education is the subject of an annotation on page 802.

Cancer is not necessarily incurable.

Early detection and treatment give the patient the best chance.

Cancer is not infectious nor contagious. Doctors and nurses do not catch cancer from their patients. There is therefore no need to be afraid of visiting or caring for anyone with the disease.

As a general rule cancer is not hereditary, and the fact that cancer has occurred in a family is no cause for anxiety.

Cancer is usually painless at first. Later it may cause pain when it interferes with an organ or presses upon nerves.

Everyone should know the warning symptoms and consult the doctor without delay if any of them appear. They may not prove to be caused by cancer, but it is a wise precaution to have medical advice.

Continuing our Phonodiary special edition, the Marie Curie Memorial Foundation counsels you to see your doctor about any of the following symptoms:

1. A painless lump in the breast.
2. A discharge or bleeding from the nipple.
3. Any irregular or unusual bleeding from the womb. (Especially after the "change of life.")
4. A sore place, especially in the mouth or on the face which does not show signs of healing in three weeks.
5. Bleeding from the bowel. (This may be caused by piles, but it is wise to make sure.) Also get a doctor's advice about any unusual change in the bowel's habit.
6. Blood in the urine.
7. Persistent indigestion with loss of appetite.
8. A persistent cough or hoarseness which lasts more than four weeks.
9. Difficulty with swallowing.
10. Any increase in size, deepening in colour, or bleeding of a wart or mole.

These symptoms do not necessarily mean cancer, but they should, in any case, be promptly investigated.

You have no need to be ashamed of cancer. It occurs in every type of family.

ST. MARY'S HOSPITAL MEDICAL SCHOOL

CENTENARY DINNER

More than 400 members of the staff and student body, past and present, assembled for the centenary dinner of St. Mary's Hospital Medical School on September 25. The EARL OF VERULAM, president of the School, opened the proceedings by presenting to Roger Bannister, a newly graduated student of St. Mary's, and to two of his competitors and friends in athletic achievement, C. J. Chataway and C. W. Brasher, copies of Sir Zachary Cope's book, *The History of St. Mary's Hospital Medical School*. The citation stated that this was to mark the occasion of the one-mile race at Oxford on May 6 last, when Bannister set up a world record.

Role of the Medical Schools in a State System

Sir RUSSELL BRAIN, P.R.C.P., who proposed the health of the School, said that more rapidly than ever before in the case of an undergraduate medical school St. Mary's had achieved world-wide renown. The first reason for this was the contribution to medical science which had been made from its laboratories; the second, the long line of distinguished teachers and students who had been associated with the School, and the third—perhaps the chief—the steady flow from its doors of all-round well-trained doctors. Sir Russell went on to pay a tribute to the deanship of Lord Moran (1920–45), and said that if a school was a living organism it was a nice problem where in the nervous system the dean of a medical school should be localized. Some would say in the speech centre, but he had no doubt that Lord Moran had been localized in the motor cortex, with a considerable extension into Broca's area. It was the energy, farsightedness, and persuasiveness of the then Sir Charles Wilson which had made a unique contribution to the fortunes of the School, and it was not difficult to forecast that this prosperity would continue. The prosperity of medical schools was more important to-day than ever before. "We live in an age dominated by the growing power of the State. All revolts in English history have been against excessive concentration of power. If medicine to-day is not to be engulfed by the State we must strengthen those authorities in medicine which are independent of the State, and the medical schools here have a part to play, because they are the meeting-point of two such authorities—namely, the universities and the Royal Colleges."

LORD VERULAM, in response, referred regretfully to some staff changes, in particular to the retirement that very day of Professor W. D. Newcomb, who had been head of the department of pathology for some 30 years and deputy dean for 10 years. Through the operation of the age limit they had also lost Dr. Roche Lynch and Mr. Williamson-Noble. But in spite of changes he could say that the future of the School was bright. If research was to go on both freedom for research and funds for it must be ensured. The School was shortly launching a great appeal campaign for extension of research and teaching facilities. On the teaching side he believed that distantly on the horizon might be seen the possibility of an over-production of medical men. If that was true it meant that at the highest level a great deal of clear, independent thinking would be required to see the way through and around the many difficulties which lay ahead, only a few of which could possibly come within his own powers of perception. But it would be fatal if all the thinking was to be done by the politicians. There was here a field for research in what might be called administrative medicine—medicine adjusted to the social and economic needs of the time—and in this research he hoped that some son of St. Mary's would make his mark.

Mr. R. M. HANDFIELD-JONES, senior surgeon to the hospital, proposed the health of the guests, who included the Presidents of the three Royal Colleges and of the College of General Practitioners, the Vice-Chancellor of London University, the deans of several other medical schools, and the Mayor of Paddington. Sir HARRY PLATT, P.R.C.S., who responded, spoke humorously of the qualities he had found most required in his new office at Lincoln's Inn Fields. He conceived them to be "the eye of an accountant, the hand of a professional mendicant, and the courage of a company promoter," but he also mentioned the pleasure it gave him on his first day as president to enter his room and find 200 diplomas awaiting his signature, and the one at the top bore the name of Roger Bannister of St. Mary's.

Mr. A. G. CROSS, the present Dean, proposed the health of the Chairman, and with that the proceedings should have come to an end, but there were cries for Lord Moran and for Mr. Dickson Wright, and both responded in a witty reminiscent vein, LORD MORAN remarking that the wise dean would not unduly dwell on the past but would recognize that each generation of students had to carve its own path; while Mr. DICKSON WRIGHT said that he had never known the students of St. Mary's, both men and women, and the staff to be on better terms with each other than now.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Smoking and Lung Cancer

SIR,—We find Professor Sidney Russ's memorandum on smoking and lung cancer (*Journal*, September 4, p. 578) most obscure, both in its logic and its arithmetic. He seems, however, to be making two main points, (1) that the risk of a smoker getting lung cancer is small (even if the causation be accepted); (2) that there must be other, and by inference more important, factors in the production of the disease since no exact relationship has been demonstrated between the levels of lung cancer mortality and of cigarette consumption in different countries of the world. So far as we understand his arithmetic he arrives at the first conclusion by estimating the ratio between the number of men with lung cancer *at a given moment* who smoke a given amount of tobacco and the number of men in the population who at that same time smoke that amount. He then assumes that this is the same as the proportion of men who develop lung cancer at any time in their lives. It seems to us akin to saying that because in a given year only 1 in 1,000 persons has influenza, influenza must be a rare disease and only 1 in 1,000 persons will ever get it. While wholly rejecting that reasoning we would admit that sufficient data do not at present exist to allow precise statements of the risks. On the basis of our own figures Heady and Barley[1] have calculated that for a smoker of 25 cigarettes a day the risk of contracting lung cancer before the age of 75 years would be about 9 in 100. A figure of that order is hardly negligible.

Professor Russ arrives at his second conclusion from a graph tentatively put forward by one of us (R. D.) to show such data as were available from six countries. He objects to the customary scientific procedure of plotting the data on a graph and drawing the best-fitting straight line through them, and since two of the points diverge from the line so drawn he reaches the sweeping conclusion that "as we go from one country to another no relationship exists between cancer death rates and the degree of cigarette smoking." We are not ourselves enamoured of correlation coefficients based upon six observations, but, in fact, the figure is 0.62; for what it is worth, then, these six observations are associated to quite a high degree. To Professor Russ's dogmatic statement, we still prefer Doll's cautious comment on these scanty figures, viz.: "I doubt whether much significance should be attached to the result, but it is not inconsistent with the existence of a relationship between lung cancer and cigarette smoking." The discrepancy lies in the position of the U.S.A. *vis-à-vis* this country, and one possible

explanation of that has already been given by Dr. H. Stalker and Dr. P. Glees in your columns (*Journal*, September 18, 1954, p. 702).—We are, etc.,

RICHARD DOLL.
A. BRADFORD HILL.

REFERENCE
[1] *British Medical Journal*, 1953, 1, 1105.

Operative Cholangiography

SIR,—I was glad to read the article on operative cholangiography by Mr. E. S. R. Hughes and Mr. R. H. Kernutt (*Journal*, September 11, p. 620), as I believe that the more this method is practised the higher will be the percentage of complete cures after cholecystectomy. Any method which may diminish the number of unfortunate patients who are left with a stone in the extra-biliary passages, or some other pathological lesion following cholecystectomy, is worthy of consideration. In this article the technique of diagnostic operative cholangiography is clearly described, but I would suggest that while the film is being developed the gall-bladder should not be removed. Traction on the gall-bladder with suitable forceps is a very useful aid in steadying the liver and maintaining rotation, which assists in exposing the biliary ducts. The four or five minutes required for the development of the film are better employed in removing the appendix, as "No cholecystectomy without appendicectomy" is a surgical axiom.

The authors rightly stress that cholangiography is not burdensome, and the only time added to the operation is that required for nicking the cystic duct, injecting the contrast medium, and exposing the film—perhaps a matter of three or four minutes. This time is well spent if it obviates the necessity of exploring the common duct in a doubtful case, also the cholangiogram will display the anatomy of the ducts, which, in abnormal cases, may save the surgeon from committing errors in the subsequent dissection. I cannot agree that the risk of exploring the common duct is negligible, especially in a fat patient, or when previous inflammation and fibrosis have matted tissues together and disturbed the normal anatomy. Some authorities admit a mortality of 5% when exploration of the common duct is necessary, as compared with about 0.5% when this procedure can confidently be avoided.

Spasm of the sphincter of Oddi was apparently present in one of the 45 cases on which this paper is based. The common duct was obstructed, with no evidence of a calculus, and a fine probe was passed into the duodenum. In my opinion spasm of the sphincter is more common than is usually supposed, and it can only be diagnosed by cholangiography, as the common duct may not be dilated to such an extent as to suggest that exploration is advisable. If the obstruction is unrelieved, stasis of bile in the biliary passages persists, and infection, if present, is encouraged; probably the recurrent attacks of pain and jaundice associated with the condition are due to exacerbations of cholangitis. In addition, sphincteric obstruction interferes with pancreatic drainage and so predisposes to attacks of subacute pancreatitis, which is probably one of the causes of dyspeptic symptoms following cholecystectomy. Adequate treatment demands either thorough dilatation of the sphincter so that a Moynihan's flexible dilator passes easily into the duodenum, or sphincterotomy. The latter procedure is preferable, and is performed either with a sphincterotome or by transduodenal exposure. I have reported a series of 322 cases in which cholangiography was performed, and of these 14 required sphincterotomy.[1] Also, in addition to unsuspected stones and spasm of the sphincter, I have discovered one papilloma of the common duct and two cases of carcinoma of the pancreas which otherwise would have been overlooked. Mallet-Guy[2] in his review of 1,500 cases of cholangiography states that he would never perform an elective cholecystectomy unless facilities for this procedure were available. Nor would I.—I am, etc.,

London, W.1. R. J. MCNEILL LOVE.

REFERENCES
[1] *Brit. J. Surg.*, 1952, 40, 214.
[2] *Surg. Gynec. Obstet.*, 1952, 94, 385.

SIR,—I have read with great interest the article "Operative Cholangiography" by Mr. E. S. R. Hughes and Mr. R. H. Kernutt (*Journal*, September 11, p. 620), but, much as I admire the excellence of the article, I am afraid I cannot agree with the opinions expressed by the authors. I tried this method of investigation as far back as 1938, but, after a prolonged trial, the results were so disappointing that I abandoned it. My interest in the subject was stimulated by the many articles on cholangiography published in the U.S.A. by Drs. R. R. Best and N. F. Hicken,[1-3] who, incidentally, spoke of investigation carried out at the time of operation as *immediate* cholangiography, and investigation post-operatively as *delayed* cholangiography. Like them I made the investigation directly into the common bile duct with a needle and a 20-ml. syringe. Morphine was used in premedication because of its constricting effect on the sphincter of Oddi. The cystic duct was first ligated, the bile aspirated from the common bile duct, and the contrast medium then injected. I tried various solutions—"lipiodol," "uroselectan," and diodone ("perabrodil"). "Thorotrast," then perhaps the best contrast medium of all, was considered but advised against on account of its potential radioactive properties. Although I had the help of skilled radiologists none of the pictures were really satisfactory, and I have yet to see published, in this country at any rate, clear pictures of cases which left no doubt about the abnormality present. I refer particularly to stones in the common bile duct, and my investigations were carried out not to ascertain if there were stones in the duct but as to how many stones were present, so that none should be overlooked. During operation it is a tedious wait for the *x*-ray film or films to be developed, but, as the authors say, the tedium can be whiled away by proceeding with cholecystectomy or, as Mr. McNeill Love[4] wisely suggests, appendicectomy. However, the results in my experience were disappointing and in some cases misleading. So I gradually tired of it, and finally abandoned it. As Mr. Rodney Maingot[5] says, the investigation is "cumbersome, useless, and misleading." Let us hope that the introduction of newer preparations like "biligrafin" given intravenously will help to solve our difficulties *before operation*. Biligrafin contains approximately 64% of iodine and outlines not only the gall-bladder but also the bile ducts. Unfortunately, the best pictures of the bile ducts are obtained in patients who have had their gall-bladders removed, which is not exactly what we want. Better pictures of the ducts can be obtained post-operatively by the introduction of the contrast medium through a T-tube.

Nor do I agree with the authors' opinion with regard to post-operative or delayed cholangiography. I think this is a most valuable procedure, and here I think the authors are somewhat confused in quoting the article by Hicken and others[3] as being in favour of immediate cholangiography; the article in question, published in the *Archives of Surgery*, dealt exclusively with post-operative cholangiography.

Exploration of the common bile duct entails drainage of the duct, preferably by T-tube, and post-operative cholangiography should be carried out through the tube to ensure that all is well. Over the past sixteen years I have personally carried out this investigation in more than 200 cases of stone in the common bile duct and in three cases found that I had left a stone behind, and this in spite of careful search, the passage of bougies into the duodenum, syringing of ducts, and suction. In one of these cases the stone passed eventually into the duodenum after treatment, but in the other two no treatment availed. In these the patients did not resent a second operation when the situation was explained; in fact they welcomed it when they were assured that they would be rid of their trouble. The T-tube proved a welcome guide to the common bile duct in these cases, and rendered the operation easier.

No, I consider that post-operative investigation through a T-tube is a most salutary precaution. Overlooked stone in the common bile duct brings discredit on the operation of cholecystectomy and this investigation goes a long way

to remedy this. You were kind enough to grant me space on this subject in the *Journal* in 1941.[9]—I am, etc.,

London, W.1. MICHAEL J. SMYTH.

REFERENCES

[1] *Surg. Gynec. Obstet.*, 1935, **61**, 721.
[2] Ibid., 1937, **65**, 217.
[3] *J. Amer. med. Ass.*, 1936, **107**, 1615.
[4] *Surg. Gynec. Obstet. (Int. Abstr. Surg.)*, 1938, **66**, 126.
[5] Ibid., 1938, **66**, 1040.
[6] *Brit. J. Surg.*, 1952, **40**, 214.
[7] *Ann. roy. Coll. Surg. Engl.*, 1952, **10**, 97.
[8] *Arch. Surg. (Chicago)*, 1950, **60**, 1102.
[9] *British Medical Journal*, 1941, **1**, 111.

Galactosaemia

SIR,—We have read with interest the articles by Drs. P. J. N. Cox and R. J. P. Pugh (*Journal*, September 11, p. 613) and by Drs. M. W. Arthurton and B. W. Meade (p. 618) and the annotation (p. 640) on galactosaemia, and would like to make the following comments based upon our own observations. We believe that it is imperative to remove all lactose or traces of galactose from the diet of the very young infants suffering from the disease, and we have found that the quantity of lactose in "casilan" is excessive for such infants. We know that in three infants in whom the diagnosis was made early in life and correct dietary measures taken the subsequent mental and physical development has been perfectly normal. Finally, we would point out that evidence is already available to support a renal leak of amino-acids[1] which is almost certainly due to the toxic effect of galactose on the kidney tubules.—We are, etc.,

GEORGE KOMROWER.
Manchester, 3. ARON HOLZEL.

REFERENCE

[1] Komrower, G. M. (1953). *Arch. franç. Pédiat.*, **10**, 185.

SIR,—My attention has been called to the article on galactose diabetes by Drs. Edward G. Fox, W. Morton Fyfe, and Arthur W. Mollison, published some months ago (*Journal*, January 30, p. 245), which I regret to say escaped my notice at the time. I have also read the articles by Drs. P. J. N. Cox and R. J. P. Pugh (*Journal*, September 11, p. 613) and by Drs. M. W. Arthurton and B. W. Meade (p. 618). In their papers the authors give an account of the methods generally used for the identification of a copper-reducing substance present in the urine as galactose. In this connexion I should like to mention a mycological method I introduced many years ago which can be carried out in various ways, including the following two.

(1) A certain amount—about 15 or 20 ml.—of the copper-reducing, freshly passed urine is sterilized (in practice boiling for one minute is sufficient, and does not alter the chemical structure of the sugar) and placed into two tubes, each containing a Durham's fermentation small tube, or into two saccharometers. It is of advantage to add one-third the volume of sterile, sugar-free peptone water as found in all bacteriological laboratories to facilitate the growth of the diagnostic organisms. Tube 1 is inoculated with *Proteus Morgani sensu stricto* (does not touch maltose or pentose), in the past known as Morgan's bacillus No. 1. Tube 2 is inoculated with *Candida Krusei* (*Monilia Krusei*). If after two or three days of incubation at 35–37° C. tube 1 (*Morgani*) contains gas and tube 2 (*Krusei*) does not, the inference is that the copper-reducing substance present is galactose. This is easily understood by keeping in mind the fermentative reactions of the two organisms.

With regard to the copper-reducing sugars which may be found in the urine—viz., glucose, laevulose, maltose, galactose, pentose, and lactose—*Proteus Morgani sensu stricto* (Morgan's bacillus No. 1) produces fermentation with gas only in glucose, laevulose, and galactose (not in maltose, lactose, pentose), and *Candida Krusei* produces fermentation with gas only in glucose and laevulose (not in maltose, lactose, galactose, pentose). The urine has been fermented by *Proteus Morgani sensu stricto*, and therefore the copper-reducing substance present can only be glucose, or laevulose, or galactose, but, had it been glucose or laevulose, it would have been fermented also by *Candida Krusei*; therefore the copper-reducing substance present must be, in all probability, galactose. The above can be condensed in the following formula:

Fehling or Benedict	+	} = galactose
Proteus Morgani sensu stricto	+	
Candida Krusei	0	

(2) Same technique as above, but tube 1 is inoculated with *Candida macedoniensis* and tube 2 with *Candida Krusei*. If fermentation with gas occurs in tube 1 (*macedoniensis*) and not in tube 2 (*Krusei*) we can come to the conclusion that in all probability the copper-reducing substance present in the urine is galactose. The reason is that with regard to the usual copper-reducing sugars, which may be found in urine—namely, glucose, laevulose, maltose, galactose, pentose (usually arabinose)—*Candida macedoniensis* produces fermentation with gas only in glucose, laevulose, galactose, and therefore the copper-reducing substance in the urine must be either glucose, or laevulose, or galactose, but, had it been glucose or laevulose, the urine would have been fermented also by *Candida macedoniensis*, and therefore the copper-reducing substance must be, in all probability, galactose.

Fehling or Benedict	+	} = galactose
Candida macedoniensis	+	
Candida Krusei	0	

The reader interested in the mycological detection and identification of various sugars, and other carbohydrates, both copper-reducing and not copper-reducing, may find it advantageous to consult some of my old papers on the subject, among which are the very first one published jointly with Dr. F. E. Taylor as long ago as 1917[1] and a very practical one published in 1931 in the *Journal of State Medicine*.[2] Cultures of reliable strains of most of the organisms, fungi, and bacteria used in these methods are available, and I shall be pleased to send them to medical men and laboratory workers desiring them.—I am, etc.,

Lisbon, Portugal. ALDO CASTELLANI.

REFERENCES

[1] *British Medical Journal*, 1917, **2**, 855.
[2] *J. State Med.*, 1931, **39**, 621.

Visit to Poland

SIR,—I should like to comment shortly on the letter from Dr. Wladyslaw Tacreiter (*Journal*, August 21, p. 466). He appears to resent very much the fact that I found quite a lot to commend in the way the authorities in Poland are tackling the enormous problems which faced them at the end of the war. For some reason he thinks I was prejudiced and thus was beguiled in thinking things better than they really are.

I am not a Communist and, in fact, belong to no political party. I do belong to the Medical Association for the Prevention of War (which, incidentally, I commend to all members of the medical profession, including Dr. Tacreiter), and I consider that by pointing out that everything is not black behind the so-called "iron curtain," nor everything white on this side of it, I may be serving the cause of peace. The statistics I quoted in my letter were given to me in Poland, the ones on tuberculosis by the superintendent of the sanatorium for children which I visited in company with other doctors, architects, teachers, etc.—all men and women of integrity. I saw no reason why I should query them. All the doctors I met in Poland struck me as men and women devoted to their work, and they made no secret of the enormous problems with which they were confronted. Certainly none of them seemed at all inclined to throw up the sponge and seek easier conditions.

I am rather amused that Dr. Tacreiter saw fit to bring out once more the old cliché that the sanatorium I saw was the only one I was "allowed to visit." I have travelled quite extensively in Europe and other continents, and I have yet to meet the nation which shows visitors the worst and not the best of their institutions. Not being entirely gullible, I of course realized that it was highly unlikely that all other facilities were of the same excellent standards as the ones I saw. The fact remains that the authorities have a high standard towards which they are striving. No doubt Dr. Tacreiter is right in saying that doctors are in such short supply compared with the need that time devoted to

patients must be rationed. May I suggest, Sir, that you print in your journal an article on medicine in Poland, similar to the recent very interesting one on medicine in Russia? Finally, may I recommend to your readers a book entitled *Soviet Psychiatry*[1] by an American, Dr. Wortis, which is in the B.M.A. library, and which is most enlightening on life in general in a communist country?—I am, etc.,

Dunmow, Essex. WINIFRED M. COPPARD.

REFERENCE

[1] *Soviet Psychiatry*, 1950. Baltimore.

Infant-feeding

SIR,—Dr. R. A. de K. Glover (*Journal*, September 11, p. 645) in his reply to my letter in your issue of August 28 (p. 535) contends that the opinions quoted in the infant-feeding advertisement are a "reasonable cross-section of medical opinion," but I submit that he has not disproved my argument that they are outdated and impractical. Dr. Charlotte Naish, Professor R. S. Illingworth, and Dr. Ian Wickes approach the subject by careful study of large series of cases, and their conclusions are therefore more scientific than the dogmatic teaching in most textbooks.

However, the convincing test is with one's own patients, and my experiences in hospital paediatrics, with Army families, in general practice, and with my own children have left me with no faith whatsoever in the strict schedules of the majority of textbooks. It seems that Dr. Glover has misunderstood his quotation from Dr. W. Sheldon, about starting consecutive feeds on alternate breasts. This is quite different from using only one breast at each feed—the method I criticized as leading to a decreased supply, and thence to the bottle. Very often artificial feeding is a sign of poor advice (or none at all), and its prevalence to-day is a sad reflection on the teaching of medical students, nurses, and health visitors.—I am, etc.,

Wem, Shropshire. ARNOLD GEORGE.

Negative-pressure Drainage in Radical Mastectomy

SIR,—We have been using negative-pressure drainage in radical mastectomy cases for nearly two years at St. James's Hospital, Balham, and agree with Mr. Gordon F. Cassie (*Journal*, August 21, p. 452) that this method gives most gratifying results. In place, however, of the underwater suction described by Mr. Cassie we connect the tube to a low-pressure electric suction machine, maintaining a continuous negative pressure of 2 to 3 cm. of mercury.

This method avoids the necessity for daily aspiration of air from the tube and ensures a constant and steady negative pressure. Its main advantage, however, is that an exact measurement of the fluid draining from beneath the skin flaps can be made, as the tube drains into an empty bottle. The tube is removed when no further drainage occurs, often within 48 to 72 hours of operation; it is often unnecessary to continue drainage for the five days specified by Mr. Cassie—every day that the tube remains *in situ* increases the risk of infection entering through the unhealed stab wound. Occasionally, however, serous fluid continues to collect for considerably longer than five days, in which case the suction is continued as long as necessary.—I am, etc.,

London, S.W.12. CAREY C. K. SMITH.

Urology at St. John's Hospital, Lewisham

SIR,—The above hospital has about 100 beds. During the last 30 years or so of its existence as a voluntary hospital it was served by the special departments which usually function in a well-organized general hospital. Up to the present these specialties—which have included urology throughout the above-mentioned period—are still active and have always set a high standard of hospital service.

It is now learnt that it is the intention of the Minister of Health no longer to permit the treatment of urological cases there and to close the corresponding special department. I wish to protest against this intention, because its fulfilment would be a harmful step against the public interest.

In the voluntary hospital days, once a special department was established at a hospital it was there to stay. No doubt the Minister has some purpose of regional policy which makes him feel justified in not allowing this principle to be followed: but his attention should be called to certain embarrassments which will follow:

1. Although the general practitioners of the neighbourhood will doubtless be instructed to send their urological cases elsewhere, many new cases will arrive at St. John's on their own initiative, for patients commonly reach hospitals in this way.
2. Urological cases are universally dealt with at general hospitals, and it will be impossible to prevent this continuing at St. John's. Therefore it must be considered a retrograde step to close the urological department.
3. Some emergency urological cases are bound to continue to arrive at St. John's, and it will certainly be unwise not to give them attention on the spot.
4. Removing this special department, because it will reduce the scope of the training for nurses, is going to increase the matron's difficulty in keeping the hospital properly staffed.

One hopes that a careful consideration of these points will induce the Minister to have second thoughts.

Finally, let me make my personal position clear. At the end of this month I shall be in partial retirement as a hospital consultant, and this change will conclude my attendances at St. John's. I am, however, looking forward to this relaxation, just as much as I have enjoyed my long association with this splendid little hospital.—I am, etc.,

London, W.1. H. P. WINSBURY-WHITE.

Normal C.S.F. Sugar in Tuberculous Meningitis

SIR,—Dr. J. G. Alexander (*Journal*, September 11, p. 646) reports a case of tuberculous meningitis which had a normal cerebrospinal fluid sugar on admission to hospital. As he points out, it is indeed important that it should be widely known that this can happen. We have had three such cases among the past 50 patients with tuberculous meningitis. This may partly be due to the fact that we see these patients in hospital earlier these days, although the sugar level by no means bears a constant relationship to the clinical stage of the disease.

Nevertheless the cerebrospinal sugar level remains an extremely valuable pointer in a case of doubtful meningeal irritation, and a reduced figure in a predominantly lymphocytic fluid is strongly suggestive of tuberculous meningitis. In a patient with possible tuberculous meningitis but a normal sugar it is essential to carry out daily lumbar punctures and repeated, prolonged search for organisms. It is most unusual for the sugar level not to fall below normal at some stage of treatment, and we have only seen this once in a series of over 140 cases.—I am, etc.,

Pill, nr. Bristol. G. D. W. MCKENDRICK.

Incoagulability of Blood after Accidental Haemorrhage

SIR,—We have read with interest the article on this subject by Dr. H. C. Moore (*Journal*, July 31, p. 277), but feel that it is apparently not sufficiently realized in this country that post-operative incoagulability of blood can occur after various surgical operations and is not confined to obstetrics. The subject has been dealt with in a series of articles in *Revue d'Hématologie*,[1 2 3] where it is pointed out that, in addition to obstetrical conditions, it is particularly liable to occur after operations on the lungs and brain. During the past two years five cases have come to our notice in this city; two were in pregnant women, one followed a lobectomy and thoracoplasty, and one followed a gastrectomy. The fifth followed a prostatectomy, and we would like to describe this case in detail.

On March 24, 1953, after a three-day course of chloramphenicol a man aged 80 underwent a transvesical prostatectomy

for increasing difficulty of micturition due to benign hypertrophy of the prostate (subsequently proved histologically). His condition was good and there was nothing of note in his previous history. During the operation his blood was observed to clot in the normal way. The operation was concluded without incident and his immediate post-operative condition was excellent. Three and a half hours later bleeding recommenced from the incision. Some deep sutures were inserted in an attempt to control this. Oozing started also from the drainage tube and soon developed into profuse haemorrhage. Two ampoules of vitamin K were injected and preparations were made for a blood transfusion, but the patient suddenly collapsed and died five hours after the conclusion of the prostatectomy. The estimated blood loss was 4 pints (2.3 l.). At necropsy it was found that blood had seeped through the subcutaneous tissues from the incision and had reached the dorsum of the body. The prostatic bed and the whole of the bladder mucosa were very haemorrhagic. Apart from a small clot 1 cm. diameter in the left ventricle, the blood throughout the body was liquid. All other organs were in a very satisfactory state for his age.

As soon as the bleeding began a sample of blood was collected by venepuncture and sent to the laboratory for cross-matching. This sample failed to clot, and in fact had not clotted the next day. Unfortunately the blood sample was only small (less than 2 ml.), but when it had not clotted after half an hour at 37° C. it was divided into two specimens. Thromboplastin was added to one of these without any effect. A drop from the other was added to some normal blood and it was found that the coagulation time of this was thereby shortened to 3½ minutes (Lee and White's method). Liquefaction of the clot was observed 30 minutes later and was complete after a further 30 minutes.

It is not always easy to investigate these patients owing to their serious clinical condition, but the diagnosis should be suspected when a venepuncture sample fails to clot and the patient gives no history of a haemorrhagic disorder. We do not believe that there is any reliable laboratory test which will forecast the occurrence of the condition. If the intravenous injection of fibrinogen is proved to be efficacious, then the phenomenon is probably sufficiently common to warrant there being a supply of fibrinogen immediately available in all maternity and large general hospitals. We are grateful to Dr. R. G. Macfarlane for drawing our attention to the articles in *Revue d'Hématologie*. —We are, etc.,

W. N. Rollason.
A. J. Shillitoe.

Hull, Yorks.

References

[1] *Rev. Hémat.*, 1952, 7, 3.
[2] Ibid., 1952, 7, 20.
[3] Ibid., 1952, 7, 30.

Pilonidal Sinus

Sir,—With reference to the leading article "Pilonidal Sinus" (*Journal*, September 18, p. 694), no mention is made of the simplest method of closure of the "dangerous dead space" following excision of the involved area, by the use of a split skin graft. The procedure was described in the *Postgraduate Medical Journal*[1] in August, and encourages adequate excision without the worries of closure by direct apposition or complicated rotation flaps. This method eliminates the risk of recurrence by removing the hair-bearing skin; it also obviates a long stay in hospital and the necessity for prolonged dressings.—I am, etc.,

D. Wynn-Williams.

East Grinstead, Sussex.

Reference

[1] *Postgrad. med. J.*, 1954, 30, 430.

The Dormant Cancer Cell

Sir,—Professor Geoffrey Hadfield's paper on "The Dormant Cancer Cell" (*Journal*, September 11, p. 607) supplies convincing proof of the ability of protoplasm to survive incredible degrees of cold for long periods unharmed but supplies no proof that similar changes occur at body temperature. He describes the small highly refractile spherical bodies in which no nuclei are visible which Craigie found in tumours maintained at −70° C. for months. Craigie gave to these bodies the name "paramorphic" cells, and he found that, on thawing, these cells may undergo mitosis and reproduce the tumour from which they are derived. Professor Hadfield thinks that only the paramorphic cells survive the ordeal by freezing, though he admits that proof is difficult. He then turns to an entirely different problem—namely, the long period which may elapse between an operation on a human malignant tumour and recurrence of the tumour—a period which may vary between a few months and 30 years. "When the interval is prolonged to six years or more it seems impossible to escape the conclusion that the cells of the dormant growth are in a state of *temporary mitotic arrest*." Such dormant cancer cells, he thinks, may be found in relation to the scar or in the gland and may be kept dormant by anoxia, or by the pressure of fibrous tissue. So much may be admitted. A third situation in which dormant cancer cells may be found and may be reactivated is in deeply placed organs. "Such foci must have been originally implanted before excision of the primary growth," surely a most improbable assumption in cases where the patient survives for years in good health.

It is at this point that Professor Hadfield's thesis breaks down. He has misconceived the process of dissemination. He apparently believes that visceral metastases are always

due to lymphatic, venous, or arterial embolization. He ignores completely the insidious but deadly process of permeation which is often a dominant factor in the later stages of dissemination. For years tendril-like lines of proliferating cancer cells may push their way through the capillary lymphatic vessels around the primary growth. The choked lymphatics are distended until they rupture, an event which excites a vigorous inflammatory reaction which as a rule locally destroys the cancer cells. But meantime the advancing microscopic edge of the growth has passed on like an invisible ringworm, often without giving any clinical sign of its presence for years, until it invades one of the serous cavities. When this happens visceral metastases rapidly ring down the curtain. There is no evidence of "mitotic arrest" but rather of continuous slow proliferation of cancer cells, and of their destruction, except at the microscopic growing edge, by an inflammatory reaction. Permeation is not a theory, but a fact.

The annexed photograph from a case of carcinoma shows in transverse section several larger permeated lymphatic vessels (A), and in longitudinal section a small permeated lymphatic (B), which could not possibly have been produced by embolism.—I am, etc.,

W. Sampson Handley.

St. Olaves.

Sir,—The publication of Professor Geoffrey Hadfield's Kettle Memorial Lecture entitled "The Dormant Cancer Cell" (*Journal*, September 11, p. 607) prompts me to record a case of carcinoma of the bladder in which there has been no extension of the main part of the growth for at least 10 years.

In 1941 the patient, a man aged 54, was cystoscoped for haematuria. It was observed that he had a large growth on the right lateral wall of the bladder and a small separate one at the internal urinary meatus. The latter was treated by cystoscopic diathermy on a number of occasions, but by 1944 difficulty in micturition had increased, so it was decided to perform suprapubic cystotomy. The obstructing mass was excised together with a small piece from the large growth. On microscopic examination this proved to be a transitional-cell carcinoma. Treatment by partial cystectomy would have necessitated removal of two-thirds of the bladder and its separation from the urethra.

After the operation the patient was kept under constant observation. There was never any evidence of clinical extension of the growth of the right lateral wall, but in 1952 the disease recurred at the internal meatus associated with severe haematuria, which made cystoscopic diathermy impossible. Once more the bladder was opened and this portion of the growth removed. Since this date there has been nothing to indicate any extension of the disease, and in spite of intermittent haematuria the patient remains in good health. Apart from the two operations he has never missed a day's work owing to ill-health and never missed his week-end golf. Enforced retirement this year owing to age has caused him much more annoyance than the presence of blood in his urine. There is some value in the conservative treatment of vesical carcinoma.—I am, etc.,

London, W.C.2. A. Clifford Morson.

Sir,—As suggested by Professor G. Hadfield in his informative article (*Journal*, September 11, p. 607) there is indeed something common to frozen and dormant cancer cells—namely, restriction of the average nitrogen balance of such cells to zero, or a value close to zero. Even a small positive nitrogen balance, continued long enough, must result in cell growth through protein increase, and even a small negative nitrogen balance, sufficiently prolonged, must end in death from loss of protein. Only the static zero nitrogen balance of sub-zero temperature allows any cell to survive indefinitely in the absence of growth. At higher temperatures, however, a dynamic nitrogen balance may be so close to zero—that is, nitrogen equilibrium—that cells may survive for decades without growth. In the human brain, for example, a nerve cell may live for a century or more without enlarging or dividing, and to do this the cell must maintain an average nitrogen balance very close to zero. These conclusions, which were arrived at through early nutritional studies, have been confirmed by more recent investigations with radioactive isotopes.[1 2 3]

If dormant cancer cells are removed from the body and placed in a suitable tissue culture medium they will cease to be dormant, and will grow until environmental conditions bring further cell division to a halt. The factors responsible for dormancy of cancer cells *in situ*, as well as for restriction of the growth of normal cells, must therefore be sought in the organism as a whole, particularly with reference to its regulated tendency to nitrogen retention. A method of measuring an individual's tendency to nitrogen retention will be described in a further communication.—I am, etc.,

Sevenoaks, Kent. R. L. Worrall.

References

1 Allison, J. B. (1949). *Advanc. Protein Chem.*, **5**, 155.
2 Himsworth, H. P. (1946). *Proc. roy. Soc. Med.*, **40**, 27.
3 Moore, F. D., and Ball, M. R. (1952). *The Metabolic Response to Surgery*. Thomas, Springfield, Ill.

Detecting Lung Cancer

Sir,—The leading article entitled "Detecting Lung Cancer" (*Journal*, September 4, p. 582) touches on a subject which is giving me much anxiety. My position is almost identical with that of the clinical pathologist quoted in the article—namely, that I am fully convinced of the importance of cytological examination of sputum, but I have not the facilities to offer this investigation to my clinical colleagues. Further, I think the method should be readily available under the N.H.S., not necessarily for those cases which are fairly obviously carcinoma, but particularly for the early doubtful cases from which group one hopes to get a high proportion of operable cases. To provide an adequate service of this sort requires a small but specialized unit, including a cytologist and one or two whole-time trained technicians. There seems to me to be little doubt that we ought to provide the service, but one must be so careful that it is adequate to include the early case and not be limited to the (admittedly numerous) patients whose diagnosis is commonly settled by other means. I feel that there is also room for investigating the best type of unit to supply the needs of the provincial hospital services.

I think this is a matter which should engage the attention of one of the cancer research organizations. I should like to suggest that a small unit such as I have described might operate for a time in this district in order to gather information on the value of the method when applied "in the field" and on the best type of unit in relation to population density for this service. We in this laboratory serve a population somewhat larger than that mentioned in the article, partly rural but mostly industrial, and the two can easily be separated. We have keen, efficient thoracic surgical and chest physician units. There is a vast amount of sickness due to chronic lung diseases; air pollution is severe in half our area and absent in the other half. It is my opinion that an investigation of this type would be extremely valuable from the scientific, humane, and economic points of view.—I am, etc.,

Wolverhampton. A. G. Marshall.

Sir,—It is unfortunate that your admirable leading article on the diagnosis of lung cancer (*Journal*, September 4, p. 582) is marred by an exaggeration of the difficulties of cytodiagnosis. A five-year survival rate of 25.5% is very good, and would be better if surgeons received the cases earlier. Early diagnosis depends mainly on confirmation of clinical suspicions by sputum cytology and bronchoscopic investigations. The latter should include cytology of the bronchial exudate, histology of the bronchial exudate, and biopsy.

There are a number of difficulties in practice, but these do not include lack of time by available staff. The Derbyshire Royal Infirmary serves at least half a million people. Papanicolaou smears are taken on most new gynaecological patients; I am able to examine all these as well as the sputa without additional staff or dropping other aspects of pathology. It is quite easy to look at every cell on a slide in four minutes. A few slides present special difficulties and take longer, but rather more could be examined in safety much more rapidly with the aid of the 1¼ in. (3.7 cm.) objective. Cytological methods undoubtedly give valuable results in everyday practice. We are backward in cytodiagnosis for two reasons: (1) prejudice, now happily dying, and (2) the belief that it is a difficult and very time-consuming method requiring a special department and staff—i.e., only suitable for large teaching hospitals.

In thoracic cytology the main difficulties are that patients are not adequately instructed and bring saliva for examination, and that chest units are often separated from the main (gynaecological) cytology unit and prepare smears badly. Fortunately the latter difficulty can be overcome. With the help of Miss B. V. Slesser we obtain (*a*) sputum before bronchoscopy, (*b*) smears of the exudate in the suspected bronchus, (*c*) a histological preparation of all the exudate remaining after the smears have been prepared, and (*d*) a bronchial biopsy. With Zenker or Suza fixation the histological and cytological appearances in the bronchial exudate are identical. The histological preparation has the great advantage of being almost always perfect; no technical skill is required to place the exudate in the fixative. We have had diagnostic appearances in the section of the exudate when all other methods have been negative. To obtain the highest percentage of correct diagnoses all methods must be used.—I am, etc.,

Derby. G. R. Osborn.

Obituary

R. BARCLAY NESS, M.B., C.M., F.R.F.P.S.

Dr. R. Barclay Ness, who was for many years on the staff of the Western Infirmary, Glasgow, and an ex-president of the Royal Faculty of Physicians and Surgeons, died at Glasgow on September 7, aged 91.

Robert Barclay Ness was educated at the Glasgow Academy and the University of Glasgow, where he graduated M.A. in 1883 and M.B., C.M. in 1887. After qualification he spent some years in private practice in Glasgow before seeking a hospital appointment. His long association with the Western Infirmary began in 1895, when he joined the staff as dispensary physician. He became visiting physician to the Infirmary in 1910, and when he retired in 1928 was appointed honorary consulting physician. He was also visiting physician to the Royal Hospital for Sick Children, Glasgow, and was associated with many other medical institutions in a similar capacity, including the Ear, Nose, and Throat Hospital and the Bellefield Sanatorium, Lanark. The son of a headmaster, he himself took a keen interest in teaching. In the Anderson College of Medicine he was appointed professor of materia medica in 1893, a post he held until 1905, when he was appointed to the professorship of the practice of medicine in the College. He was examiner to the Royal Faculty of Physicians and Surgeons and to the Universities of Glasgow and St. Andrews. His services as an administrator were freely given on the boards of management of the Western Infirmary and the Royal Samaritan Hospital for Women, which he served as chairman of the board of directors.

Elected a Fellow of the Royal Faculty of Physicians and Surgeons in 1893, he took a great interest in the welfare of the Faculty. During his tenure of the office of president of the Faculty, from 1931 to 1933, he earned the grateful thanks of the Fellows for the businesslike way he managed their affairs. The most notable achievement of his presidency was the establishment of the Library and Fabric Fund. This fund he hoped would help to add to the amenities of the Faculty Hall and serve greatly to increase the scope of the library. His many services to the Faculty were recognized when in 1949 he was elected an Honorary Fellow.

A mere recital of posts held and duties performed never conveys a portrait of the man. Dr. Barclay Ness was pre-eminently a physician. Small in stature, he was precise without being pedantic, kindly without being patronizing, and with it all he had a twinkle in his eye which endeared him to young and old alike. When age prevented him from moving far from his home his many friends called to enjoy his company and his hospitality in his delightful home in West Kilbride overlooking the Firth of Clyde or in his house in Glasgow. He lived a long life. His singleness of purpose and benevolence of heart, his patience and genial personality contributed to make it a successful and happy life. To his widow we extend our sympathy.

J. C. JEFFERSON, M.B., F.R.C.S.

Mr. J. C. Jefferson, until recently consultant surgeon to the Rochdale Infirmary and Birch Hill Hospital, Rochdale, died on September 21 after a short illness, aged 66.

Born on June 22, 1888, John Cecil Jefferson came of a Middlesex family with strong naval traditions. His father was a doctor, and he was the younger brother of Sir Geoffrey Jefferson, F.R.S. From Manchester Grammar School, where he had a successful career, rising to the sixth form and winning many prizes, he went on to the University of Manchester and entered the medical school, where he was a brilliant student. He was awarded, jointly with J. S. B. Stopford (now Sir John Stopford, vice-chancellor of the University of Manchester), the Dumville Surgical Prize. In 1911 he took the Conjoint diplomas and graduated M.B., B.S. (London), with honours, and distinction in medicine. After appointments as house-surgeon and surgical registrar at the Manchester Royal Infirmary he proceeded to Guy's Hospital, London, to study for his Fellowship, being elected F.R.C.S. in the spring of 1914. On the outbreak of war he immediately joined up and was posted to the 1st/3rd East Lancashire Field Ambulance, 42nd Division, and was sent out to Egypt. In Cairo he was appointed surgeon specialist to the military hospital at the Citadel. In May, 1915, because of the illness of his father, Dr. Arthur Jefferson, he was released from service in the Army. In the same month his father died and Mr. Jefferson took over his father's practice. He resigned from general practice in 1939, and continued practice as consulting surgeon specialist.

A recital of the many honours which he received both in his profession and in public affairs would occupy much space. The last honour he received was the conferment, *in absentia*, of the honorary freedom of the Borough of Rochdale on September 20—the day before he died. The honour was conferred at a full meeting of the town council, by whom the distinction was received with great acclamation. He was president of the Manchester Surgical Society in 1948–9, president of the Rochdale Infirmary in 1940, and a fellow of the Association of Surgeons of Great Britain and Ireland. For three years he was a member of the surgical advisory committee of the Manchester Regional Hospital Board.

In his profession John Jefferson was a surgeon of the very highest order, being pre-eminent in the surgery of the stomach. In his operative work he was quick, every step being taken with perfect technique and unerring confidence. He invariably left his mark on the patient with perfect closure of operation wounds—a point of satisfaction to the patient and the general practitioner. In his approach to the patient or the general practitioner he created an atmosphere of intense confidence, and this undoubtedly made for the wonderful respect in which he was held by the people, resulting in the presentation of the freedom of the borough. He had great wit and humour. A patient with an enormous visceroptosis was sent to his clinic for advice on the use of an abdominal belt. He wrote to the practitioner stating that "the patient really wants a tray on which to carry the mass and not a belt." This report was read to the patient; the effect was magic. A diet was adopted instead, with excellent result. In the ward and wherever he moved he invariably commanded and received great respect. He was devoted to his work, and his care and thought for all alike were profound. His thought for, and often daily visits to, his patients in hospital were emblematic of his spirit.

He impressed one as being somewhat reserved and slow in address, but when he did speak his speech was rugged, clear, and outspoken. In his moments of leisure he was a great reader of outstanding literature. On one of his cruises to the Mediterranean he packed in his bag the four volumes of Winston Churchill's history of the first world war, *The World Crisis*, and read it all through most diligently during the cruise.

His death, coming as it did when he was literally in the prime and zenith of his life and profession, was an untold tragedy. It may be appropriate to hark back to May, 1915. At that stage in his life history he gave up, or at least deferred, the great opening to his ambition of life—to enter the profession of surgery—in order to take the place of his father beside his mother and a large young family. In this act there radiated the noble character in his soul.

Mr. Jefferson leaves a widow who devoted her life to his service in a most exemplary fashion, and to her all people, great and small, who knew him give their deepest sympathy. The good works that he has done will live and be remembered.—E. H. C.

W. R. D. writes: The name of John Cecil Jefferson will be remembered as long as the hospitals in Rochdale endure. His untimely death has deprived the Manchester regional service of one of its most distinguished surgeons. He was the senior visiting surgeon to the Rochdale group, and he was almost solely responsible for the high standard of surgery which he set and maintained there. I had known him since his student days, but when I held office as adviser in surgery to the Manchester region I came again into close contact with him and his work. He was a tireless worker. Surgery with him was almost a passion: pressure had to be applied to persuade him to take holidays. His wise counsel in committees and in hospital enabled them to surmount the difficult problems which arose after 1948.

He was a rare character—gentle, quiet, with the typical Jeffersonian manner of speech, and possessed of a keen sense of humour. His personality seemed to dominate his surroundings. He came of a family of doctors—a family of which Rochdale is justly proud. During his last desperate illness the municipality in his absence conferred on him the freedom of his home town, an honour so rarely given that it indicated the exceptional respect in which he was held. It has been said, by people who know, that there was little to choose between the two brothers, Sir Geoffrey and Jack, with regard to their surgical ability and mental approach to surgical problems. If Jack Jefferson had decided to continue to work at the Manchester Royal Infirmary, where he was trained and where he became a surgical registrar, the teaching hospital would have been all the richer for his association. His father's early death made his return to Rochdale a necessity.

I think it can be truly said that he was in the tradition of some of the great names in surgery. We have witnessed the passing of a fine man. The regional board never had a more loyal and devoted servant, and his friends have lost a very lovable comrade.

WILLIAM PATERSON, M.B., Ch.B.

An earlier generation at B.M.A. Headquarters will recall with affection "Paterson of Willesden," as he was always known, a familiar figure in the council chamber and committee rooms both at 429, Strand, and afterwards at Tavistock Square. William Paterson died suddenly at his home at Harlesden, where he was living in retirement, on September 29, only a few days after the death of his wife. He had been a member of the Association for 52 years, and he was always what his friend, the late Alfred Cox, would have called "a good B.M.A. man." For twenty years he was a member of the Council, he served on innumerable headquarters committees, and in his own locality of Willesden he was honorary secretary of the Division for a quarter of a century.

William Paterson was born at Peebles on April 21, 1876. He received his training at the University of Edinburgh and at its medical school, qualifying M.B., Ch.B. in 1901. He started general practice in his native Scotland at Portsoy in Banffshire, where he was also medical officer to the Campbell Hospital for Infectious Diseases. A long and serious illness made a break in his life, and he gave up his practice and for a year or two served as a surgeon with the P. & O. Company. For this service, rendered in the early part of the first world war, he received the Merchant Marine Medal. On his return from seafaring in 1916 he bought a practice in Willesden in the north-west of London, and there spent the rest of his life until his retirement in 1949. He quickly built up a reputation as a good doctor. He was specially interested in industrial medicine, and for a time served as medical officer to a large works in his district. He was also Post Office medical officer, Civil Service referee, and medical examiner for the Prudential and other assurance companies. During the last war he was chairman of one of the Willesden medical boards.

Paterson was already a member of the B.M.A. before he left Scotland, and in Willesden he whole-heartedly threw himself into B.M.A. activities. He had not been there four years before he had become honorary secretary of the Division. In 1937 he was president of the Metropolitan Counties Branch. His connexion with the central affairs of the Association began in 1920, when he was a representative at the Annual Meeting at Cambridge, and thereafter for many years the meeting was never quite complete without a sight of his tall figure and an example or two of his pawky humour on the platform. In 1922 he joined the central Council. He was honorary secretary of the Section of Medical Sociology at the Annual Meeting in Bradford in 1924.

The range of his interests and of his service to the Association is indicated by the committees of which he was a member. The list extends to not far short of forty. His work in the Medico-Political and Public Health Committees was most prominent. His experience as a ship surgeon made him a useful member of the committee which the Association set up to improve the status of ship surgeons and to make better provision for the health of merchant seamen. His interest in midwifery and home nursing was reflected in the part he took in committees concerned with maternity and child welfare and with nursing problems. He was interested also in overseas affairs, perhaps because he had a daughter who was a matron in the Colonial Service, and he was for many years a member of the Dominions Committee and of committees dealing with the Indian Medical Service, the report of the Indian Round Table Conference, and the organization of the medical profession in India. Poor Law reform and the status and conditions of medical officers in various branches of the public service were also subjects to which he contributed much in the way of committee discussion.

Beneath his Scottish dourness he was a most likeable man and will be greatly missed.

Dr. Pearse Williams writes: Although Paterson had a large and busy practice he succeeded in combining with his work many outside activities. He was keenly interested in the nursing of patients in their homes and took a leading part in the work of the district nursing association. He helped to build up in Willesden one of the best home-nursing services in Middlesex, and an excellent example for the county health authority to follow if they have the wisdom. During the late war he was chairman of one of the medical boards concerned with recruiting and did excellent service. I became more closely associated with Paterson when I was chairman of the Willesden Division of the B.M.A. during the war years, and soon learned to appreciate his ability and knowledge and sound advice. We had our difficulties at first, as he liked to take the lead, but we soon worked amicably together, and his long experience

of medical politics was of great value during discussions on the new health service. Paterson had a long and happy married life, his wife predeceasing him by only a few days. He leaves one son and three daughters—one of whom is a matron in the Colonial Service and another an artist and trained nurse—to whom we offer our condolences. The older generation of practitioners in Willesden will remember him with affection.

C. L. BATTESON, M.R.C.S., L.R.C.P.

The death is announced at his home at Watford, after a short illness, of Dr. C. L. Batteson, who will be chiefly remembered in medico-political circles for his twenty years' secretaryship of the London Panel Committee.

Carol Luther Batteson was born on December 25, 1871. He received his medical training at the London Hospital and qualified in 1898. He worked as a general practitioner in Hammersmith until 1924, and then, having had a long experience of suburban and working-class practice, and possessing a special knowledge of the new National Health Insurance Act, into which the medical profession was then, with not a few convulsive movements, shaking down, he became secretary of the London Panel Committee. London at that time was the only committee which had a full-time secretary, and many early battles were fought out there before they reached the Insurance Acts Committee at B.M.A. Headquarters or the annual Panel Conference. Under the chairmanship of Dr. H. J. Cardale and his successors Batteson proved a most able secretary; in his quiet way he was a foil to some of the ardent spirits who made the proceedings of that committee so lively and controversial. He was a good and effective speaker and could present a case in a way which carried conviction. At successive Panel Conferences he was frequently the spokesman for London, often putting forward a minority view. In his office he was a source of constant information and help on the many problems which presented themselves in National Health Insurance. He retired from the secretaryship in 1945.

Batteson lived at Watford and took an active part in the affairs of the Watford Division of the B.M.A., being chairman in 1938–9. In the same year he became president of the West Hertfordshire Branch, and on account of war conditions his presidency was extended until 1942. He was also a member of the Watford Medical Society. He took part in the work of Association committees concerned with contract practice, and, during and after the second world war, in the affairs of the Medical War Relief Fund. Those who came into personal touch with him recall him as a businesslike, knowledgeable, and most helpful man.

We are indebted to Dr. E. A. Gregg, Chairman of Council of the B.M.A., for the following appreciation: With the passing of Dr. C. L. Batteson another link is severed with the early days of National Health Insurance. He took a prominent part in the resistance movement, and later, when the profession decided to take service, he threw himself into the work of organization immediately as a member of the London Panel Committee. His work marked him out as the man eminently suited to take up the post of secretary. He was well known and highly respected by the London insurance practitioners, who found his wise counsel invaluable in the many problems they took to him. His quiet, unassuming demeanour often concealed the real shrewdness and wisdom beneath it. He was a man of high principle and integrity and he was incapable of anything mean or underhand: his word was his bond. He was prominent in the organization of the London Public Medical Service and contributed largely to the success of that enterprise until the advent of the National Health Service brought it to a close. Even after his retirement he continued to take a lively interest in the work of the medical charities, and the Epsom Foundation especially was very dear to his heart. A wise counsellor and a loyal friend, he surely deserves the epithet "good and faithful" in a very real sense. His memory will be cherished by those of us who were privileged to know him and work with him in the Association and in the London Panel Committee, and throughout the London area by many who found in him a good and wise friend.

L. R. JANES, M.A., M.B., B.Ch.

Dr. Leonard Robert Janes, consultant pathologist at the Royal Sussex County Hospital, died in the Middlesex Hospital on September 21 after a short illness, aged 51.

Born in London on January 31, 1903, he was educated at the Haberdashers' Aske's School in Hampstead, and on winning a university state scholarship in natural science in 1920, he entered Emmanuel College, Cambridge. After taking his natural sciences tripos he proceeded to St. Bartholomew's Hospital and qualified M.R.C.S., L.R.C.P. in 1927 and subsequently took the degrees of M.A., M.B., B.Ch. Cantab. Interested in pathological research at this early stage of his career, he returned to Cambridge to work in Sir Frederick Gowland Hopkins's biochemical laboratory, and after the award of a Nita King research scholarship in pathology he worked in Professor H. R. Dean's laboratory in Cambridge.

After serving a term as house-physician at Addenbrooke's Hospital he was appointed senior assistant pathologist at the Royal Sussex County Hospital in 1930. On the late Dr. H. M. Galt's retirement in 1934 he succeeded him as pathologist. Janes was fortunate in obtaining this promotion at the early age of 31, and the 20 years during which he was head of the pathological department have seen great developments in the laboratory facilities and an ever-increasing burden of work, with consequent increase of staff. Under the National Health Service the laboratory has received official recognition as the area laboratory serving the Brighton and Lewes, Mid-Sussex, and St. Francis and Lady Chichester groups of hospitals, and the calls upon Janes's time and labours were heavy.

In recent years he returned more and more to his earlier interest in research and developed part of the Stephen Ralli laboratories for this work. He took a leading part in a programme of work on anti-epileptic drugs and the electrical excitability of the central nervous system in its more general aspects. The results of this work will be published in due course. He was much in the public eye for his medico-legal work, which has received high praise from Mr. Webb, the Brighton coroner. His great necropsy experience has been recorded in Gradwold's *Legal Medicine*, published this year. In the preface to this book Gradwold remarks that Dr. Janes's chapter entitled "Common Causes of Unexpected Deaths" is one of the most important chapters in the book.

Janes took an active part in the affairs of the Association of Clinical Pathologists, serving on the council from 1944 to 1947, and at the time of his death was president of the Channel and South-east Branch of the association and chairman of the Committee on Forensic Pathology. He was honorary secretary and later chairman of the Brighton Division of the B.M.A. and one of the divisional representatives on the Sussex Branch Council for many years. He had been honorary pathologist to the Brighton and Sussex Medico-

Chirurgical Society since 1935, and in this capacity had contributed greatly to the success of its meetings; he was an *ex-officio* member of its council, and his wise advice in the affairs of the society was much appreciated. A member of the St. Francis and Lady Chichester Hospital Management Committee since its inception in 1948, he was its vice-chairman for some years up to his death.

Despite an active professional life Janes found time for many outside interests. He was well known in Sussex masonic circles, he was a pianist of more than average ability, and he had a sound knowledge of gardening and good taste and judgment of pictures, antique furniture, and ceramics. He will be greatly missed by his colleagues and many friends, who will cherish the memory of his short and stocky figure with his impish sense of humour and chuckling laughter. Only his intimate friends might know that his gay bearing concealed a load of indifferent health, for he was a victim of asthma and must often have carried on with his work at the cost of considerable personal suffering.

His outlook on life was highly critical, and he held strong views on men and affairs with courage and tenacity; not always an easy man on committees, he inspired respect by the patent honesty of his opinions and his readiness to alter his views when convinced that he was in the wrong; but it must be admitted that he sometimes took a deal of convincing. He was unsparing in his readiness to assist his colleagues in difficult cases, and in private life was the staunchest of friends. It is indeed sad that his career should be cut short before its time, but he leaves behind him the memory of a notable figure and of a life well spent to the utmost of its capacity.

He married Georgina Donaldson Goodlet in 1929: she survives him with two daughters of the marriage, the elder a medical student, and to them a tribute of heartfelt sympathy is due.—J. R. H. T.

D. S. R. writes: Though the many friends and former colleagues of MARJORIE BACK must mourn her loss, their sorrow will be tempered by the reflection that she has been released from the long, progressive suffering and physical disability which caused her premature retirement in 1948. The details of her academic and professional career in the obituary notice in last week's *Journal* (p. 760) reveal her unusual intellectual endowments. Her mind worked quickly, and she had an accurate and retentive memory. Though her inclination lay in clerical work she was keen to demonstrate that, in the public health services at least, a woman could perform important administrative duties. That she could do this without losing the human touch was evident from the personal devotion of so many of those whose work she supervised. These continued to keep in touch with her during her last years; their visits, letters, and small tributes of affection gave her immense pleasure. Her personal attributes will ever be remembered by those who knew her. Her wisdom and critical powers, united with a dominating kindness and sympathy, enabled her to guide and advise the many who sought her advice over their problems, both human and professional. Though tolerant, if critical, of the foibles of human nature, she was roused like a lion and fought hard to rectify any miscarriage of justice that lay within her sphere. Her own loyalty and devotion to duty was clearly an inspiration to those who worked with her. Though reserved by nature, and seemingly austere to strangers, she enjoyed the good things of life and revealed to her friends a keen, sometimes puckish, sense of humour—also extreme generosity. In the difficult war years she displayed unfailing courage and selflessness. The same courage led her to fight the encroachments of her crippling illness with a tenacity which will long be remembered by those who knew and loved her.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 11** (No. 36) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	12	0	2	0		19	1	5	0	
Dysentery	219	42	159	4	2	204	24	126	1	5
Encephalitis, acute	1	0	0	0		4	0	0	0	
Enteric fever:										
Typhoid	4	0	2	0	2	6	1	0	0	
Paratyphoid	21	1	0	0		11	0	1	0	2
Food-poisoning	336	21		3		244	35		0	
Infective enteritis or diarrhoea under 2 years				6	11				17	46
Measles*	1,083	57	134	35	19	603	19	35	18	21
Meningococcal infection	24	1	12	3	2	25	0	18	1	
Ophthalmia neonatorum	30	1	2	0		41	3	4	0	
Pneumonia†	262	14	99	1		169	7	145	5	
Poliomyelitis, acute:										
Paralytic	47	0	12	0	2	92	4	20	7	9
Non-paralytic	31	2				81	6			
Puerperal fever§	210	21	10	1		223	37	15	1	
Scarlet fever	313	21	89	10	18	505	28	132	24	33
Tuberculosis:										
Respiratory	636	67	96	9				111	28	
Non-respiratory	106	8	19	3				20	1	
Whooping-cough	2,014	109	143	11	23	3,708	280	344	31	30

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0		0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years		0	1	0	2	11	0	3	2	2
Influenza	3	1	0	0	0	1	0		0	0
Measles		0	0	0	0				0	0
Meningococcal infection		1	0				0			
Pneumonia	108	21	7	7	2	105	6	19	8	3
Poliomyelitis, acute	2	0	1		0	4	0			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	59	5	9	1	2	78	6	15	4	5
Non-respiratory		2	2	0	0		1	2	0	1
Whooping-cough	0	0	0	0	0	9	1		0	0
Deaths 0–1 year	180	13	11	9	3	214	23	21	14	15
Deaths (excluding stillbirths)	4,242	615	479	109	134	4,128	524	519	128	147
LIVE BIRTHS	7,104	978	833	182	419	7,360	1047	787	205	366
STILLBIRTHS	182	16	25			154	20	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

The largest fluctuations in the trends of infectious diseases in England and Wales during the week ending September 11 were falls in the number of notifications of 492 for measles, from 1,575 to 1,083, 98 for dysentery, from 317 to 219, and 47 for scarlet fever, from 360 to 313.

The incidence of scarlet fever is very low, and during the past five weeks the number of notifications has been lower than in any week since notification began. During the week little change occurred in the local trends of scarlet fever. 2,014 cases of whooping-cough were notified, and these were 26 more than in the preceding week; the only large increases were 57 in Lancashire, from 52 to 109, and 45 in Durham, from 117 to 162. The largest falls in the notifications of measles were 113 in Durham, from 239 to 126, and 68 in Cheshire, from 134 to 66. 12 cases of diphtheria were notified, 1 more than in the preceding week. 8 of the 12 cases were notified in two cities, Liverpool C.B. 5 and Birmingham C.B. 3.

11 of the 21 cases of paratyphoid fever were notified in Yorkshire West Riding (Queensbury and Shelf U.D. 5, Dewsbury C.B. 4).

78 cases of acute poliomyelitis were notified, and these were 3 more for paralytic and 4 more for non-paralytic cases than in the preceding week. The largest returns were Essex 13 (Brightlingsea U.D. 4, Chigwell U.D. 4, Tendring U.D. 2), Yorkshire West Riding 7 (Leeds C.B. 2), Durham 6 (Sunderland C.B. 2, Felling U.D. 2), Kent 5 (Bridge-Blean R.D. 2), Lancashire 5 (Liverpool C.B. 3), Middlesex 4 (Harrow M.B. 2), and Cheshire 4 (Birkenhead C.B. 3).

The number of notifications of dysentery was the lowest for 49 weeks. The largest returns were London 42 (Islington 8, St. Marylebone 8, Southwark 8), Lancashire 36 (Liverpool C.B. 12), Essex 27 (West Ham C.B. 15), and Yorkshire West Riding 24.

The largest outbreak of food-poisoning reported during the week was 85 cases in Leicester C.B.

Quarterly Return for Scotland

The birth rate in Scotland during the second quarter of this year was 18.9 per 1,000 population, being 0.2 above the rate for the June quarter of 1953 but 0.1 below the average of the five preceding years. The infant mortality was 30 per 1,000 registered live births and was 1 above the rate for the June quarter of 1953. The death rate was 11.5 per 1,000 population and was 0.3 higher than in the preceding second quarter but 0.1 below the five-years average.

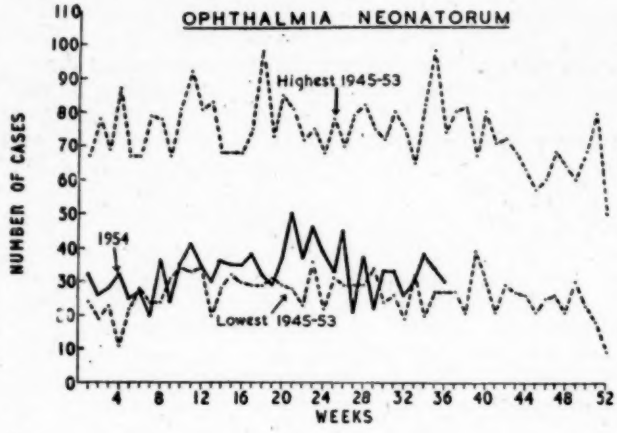
Deaths from tuberculosis were 60 fewer than in the second quarter of 1953, and of the 252 deaths 226 were attributed to respiratory and 26 to other forms of tuberculosis. The death rate from all forms of tuberculosis was 20 per 100,000 and that from respiratory tuberculosis was 18. Both these rates were 4 below the rate for the corresponding quarter of last year and they were 24 and 20, respectively, below the average of the five preceding second quarters. There were 59 deaths registered from the principal epidemic diseases, 25 fewer than in the second quarter of 1953. These deaths comprised 40 from influenza, 11 from meningococcal infections, 5 from whooping-cough, and 3 from measles. No deaths occurred from typhoid fever, scarlet fever, or diphtheria. The death rate from violence was 48 per 100,000, being 4 below the rate for the corresponding quarter of 1953. 123 of the 619 deaths were attributed to road transport accidents, a decrease of 6 compared with the preceding June quarter.

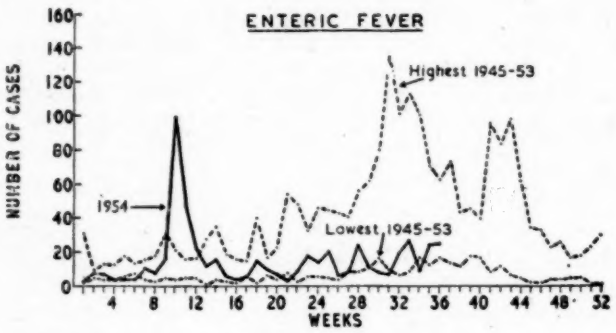
Week Ending September 18

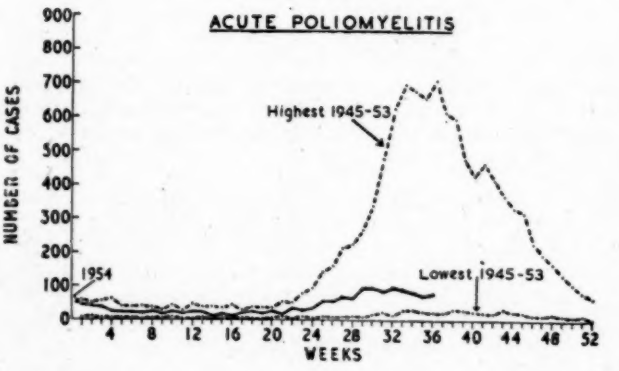
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 426, whooping-cough 1,668, diphtheria 9, measles 1,286, acute pneumonia 230, acute poliomyelitis 92, dysentery 309, paratyphoid fever 10, and typhoid fever 5.

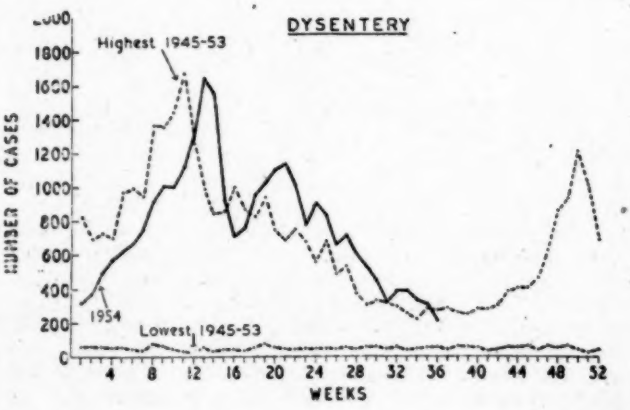
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Medical News

World Medical Association.—The eighth general assembly of the World Medical Association opened in Rome on September 27. Professor Antonio Spinelli, the distinguished Italian surgeon, was elected president for 1954–5.

Cerebral Palsy.—"The greatest achievements of preventive and curative medicine are not those which add a few more years to the tally of the septuagenarian. Rather are they those that offer to our children the prospect of the full life and the blessing of health." In these words Sir John Charles, Chief Medical Officer to the Ministry of Health, commended the study of cerebral palsy to the three-day conference on its treatment which he opened at B.M.A. House last Tuesday. The Conference was organized by the British Council for the Welfare of Spastics, and met under the presidency of Professor N. B. Capon, professor of child health at Liverpool. Intended for doctors, physiotherapists, occupational and speech therapists, and the staffs of schools for spastic children, the Conference brought together British and American workers in this field for an exchange of experience. In 1861 William Little, himself once club-footed but relieved by tenotomy, gave his classical dissertation on 47 cases of spastic paralysis before the Obstetrical Society of London; 27 years later William Osler delivered an almost equally celebrated lecture on the same subject. Contrasting Little's hopefulness and interest in active measures with the therapeutic pessimism of Osler's times, Sir John pointed out to the Conference the fallacy of supposing that the art and science of medicine advances evenly; "the curve of progress has its plateaux as well as its peaks." Progress, he continued, would be achieved only by determined study, inquiry, and research. There are signs that this determination is not lacking nowadays. Another body interested in spastic children, The National Spastics Society, formed two years ago by the parents of spastics and now with a membership of 4,000, has just launched an appeal for £45,000 to finance a five-year research programme into the causes and treatment of cerebral palsy. At a Press conference on September 23 Dr. P. E. Polani, whom the Society has appointed as full-time research physician, outlined his programme. He will work in consultation with the Society's medical advisory board, whose chairman is Professor Alan Moncrieff, and will start by surveying existing facilities and methods of treatment. Dr. Polani is at present assistant to the director of the department of child health at Guy's Hospital.

Steroid Reference Collection.—Particularly since the introduction of paper chromatography, work on steroid metabolism in Britain has been hindered by a shortage of reference compounds. The Medical Research Council's clinical endocrinology committee, helped generously by gifts of steroids from industrial firms, has therefore formed a collection of reference steroids, mostly hormone metabolites, which are now available to recognized laboratories for paper chromatography, colour reactions, infra-red measurements, mixed melting-points, and in some cases as standards for new methods of assay. It is hoped that it may also be possible to arrange an exchange of samples with the similar collection in America run by the U.S. Pharmacopoeial Convention. Details of the reference collection may be obtained from the Medical Research Council, 38, Old Queen Street, London, S.W.1. Offers of steroids for addition to the collection or requests for materials not at present included in it should be made to Dr. W. Klyne, Postgraduate Medical School of London, Ducane Road, London, W.12.

Bart's Linear Accelerator.—A 15 million-volt linear accelerator for St. Bartholomew's Hospital has just been completed in the research laboratories of Mullard Ltd. It is claimed by its makers to be the most powerful machine of its kind in the world to be used for medical purposes. The great intensity of the beam of electrons, combined with the high energy imparted to them in the accelerator, result in a very formidable source of penetrating *x* rays for super-voltage radiotherapy, particularly for the treatment of deeply-seated tumours. During the first few years, however, this accelerator will be used entirely for research, and for this reason it is now being installed in a temporary building in the Physics Department of the Medical College of St. Bartholomew's Hospital, where Professor J. Rotblat will be in charge of its operation. The research programme will include investigations on the therapeutic uses of fast electrons themselves, as well as of the neutrons which can be generated by the *x* rays, determination of the energy dissipation in tissue, and studies of the fundamental action of radiation on living tissue. In the latter investigations use will be made of the pulsed character of the electron beam, which makes it possible to produce very high doses of radiation in a time interval of about a microsecond.

New Members of the Medical Research Council.—Professor A. Bradford Hill, F.R.S., Professor G. F. Marrian, F.R.S., Professor G. W. Pickering, and the Hon. R. F. Wood, M.P., have been appointed members of the Medical Research Council.

Society of Medical Officers of Health.—Dr. Jean M. Mackintosh, of the Birmingham Public Health Department, was inducted as president for 1954–5 on September 16. Her presidential address, on the steps necessary to ensure that junior members of the Public Health Service get proper training and experience, was entitled "The Way Ahead." Dr. Mackintosh is the first woman to be president of the society since its foundation in 1856.

Medical Films.—The Kinematograph Group of the Royal Photographic Society invites the submission of medical films for an exhibition to illustrate "The Applications of Kinematography in Industry, Science, Medicine, Education, and Other Specialized Fields," which will be held in December (3–18) at the Society's House, 16, Princes Gate, London, S.W.7. The closing date for entries is October 30, but earlier notice is requested. Details from the hon. secretary, Kinematograph Group (Exhibition Committee), c/o The Royal Photographic Society.

Journal of Chronic Diseases.—The C. V. Mosby Co., 3207, Washington Blvd., St. Louis, announces the publication next January of the *Journal of Chronic Diseases*. The journal will appear six times a year, under the editorship of Dr. J. E. Moore, Associate Professor of Medicine, Johns Hopkins University School of Medicine. The annual subscription is $13.50.

Travelling Fellowship in Thoracic Surgery.—Details of a grant of $3,000 generously provided by the American Association for Thoracic Surgery for a year's study in the United States are given in our advertisement columns this week (p. 42). The closing date for applications is October 28.

Comfort Crookshank Award.—Mr. W. Sampson Handley has received the Middlesex Hospital Medical School's triennial Comfort Crookshank Award for Cancer Research. The award is valued at £230 and the prizeman also receives a medal.

World Conference on Medical Education.—The *Proceedings* will be available from booksellers next week. The book is published by the Oxford University Press (820 pp.) and costs £3 net.

News in Brief.—The Princess Royal opened an extension of the Hull Royal Infirmary at Sutton, Yorkshire, on September 24. It consists of a ward block of 116 beds, mostly surgical, and cost about £206,000.

Sir Geoffrey Jefferson, F.R.S., opened the £125,000 Midland Centre for Neurosurgery at Smethwick, Staffordshire, on September 14. The centre will serve patients from the Birmingham area.

The death of the first victim of the hydrogen bomb exploded at Bikini on March 1 was reported from Tokyo on September 23. He was one of the crew of the Japanese trawler which was contaminated by radioactive ash.

Road casualties in August, at 23,784, were the highest recorded this year, and 1,681 more than in August, 1953. The number killed was 414, a decrease of 42 on last year, but more were injured.

The National Smoke Abatement Society held its annual conference at Scarborough, September 22–24, under the presidency of Sir Ernest Smith, chairman of the Industrial Coal Consumers' Council. The Des Vœux Memorial Lecture was given by Sir Edward Salisbury, F.R.S., on "Air Pollution and Plant Life."

The Medical Group of the Institute of British Photographers held their fifth annual conference at the Royal College of Surgeons, London, September 23–26.

COMING EVENTS

Broadcasting.—"Fever Bark: The Story of Quinine," by Mr. H. Collier, Ph.D., Home Services, 9.30–10.25 p.m. Sunday, October 3.

Contraceptive Technique.—Lecture and demonstration by Mrs. Marie Stopes, D.Sc., at Mothers' Clinic, 108, Whitfield Street, London, W.1, October 7, at 2.30 p.m. No fee, tickets in advance.

Miniature Radiography Equipment.—Exhibition, in association with London meeting of directors of M.M.R. Units, at Tavistock House North (Entrance A), Tavistock Square, W.C.1, October 9, 10 a.m.–12 noon. All interested welcome.

Medical Society for the Care of the Elderly.—General meeting at General Hospital, Sunderland, October 22 and 23. Details from Dr. A. N. Exton-Smith, Whittington Hospital, Dartmouth Park Hill, London, N.19.

St. John Ambulance Brigade.—Conference for Brigade surgeons and nursing officers at B.M.A. House, Tavistock Square, London, W.C.1, October 30 and 31. Subjects on the programme include the treatment of shock, fractures, and wounds, unusual methods of transport, and artificial respiration. Further information from Department of Surgeon-in-Chief, St. John Ambulance Brigade, 8, Grosvenor Crescent, London, S.W.1.

Cardiff Postgraduate Course for General Practitioners.—November 1–6. Further details in our advertisement columns (p. 43).

Edinburgh Postgraduate Course on Induced Hypotension in Anaesthesia.—November 1–12. Further details in our advertisement columns (p. 42).

NEW ISSUES

Thorax.—The new number (Vol. 9, No. 3) is now available.

Published quarterly; annual subscription £2 2s.; single copy 12s. 6d; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Ophthalmology.—The new issue (Vol. 38, No. 10) will be available in a week's time.

Issued monthly; annual subscription £4 4s.; single copy 8s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, October 2

North-East Metropolitan Regional Tuberculosis Society.—At Nayland Sanatorium, near Colchester, 11 a.m., Joint Meeting with East Anglian Society for the Study of Tuberculosis and Diseases of the Chest. 11.30 a.m., discussion: Place of Minor "Collapse Therapy" in the Treatment of Pulmonary Tuberculosis To-day; 2 p.m., Dr. George Day: Some Transatlantic Differences in Approach; Dr. E. G. Sita Lumsden and Dr. D. F. van Zwanenberg: Sarcoidosis; Dr. C. E. P. Downes: A Few Observations Regarding Chronic Inflammatory and Degenerative Changes in the Lungs.

Monday, October 4

Institute of Psychiatry.—5.30 p.m., lecture demonstration by Dr. E. Stengel.

●Royal College of Surgeons of England.—5.15 p.m., Mr. J. E. Piercy: Surgery of the Thyroid Gland; 6.30 p.m., Mr. L. N. Pyrah: Electrolyte Imbalance in Urinary Obstruction.

Tuesday, October 5

Institute of Dermatology.—5.30 p.m., Dr. C. O. Carter: Principles of Genetics.

●Royal College of Surgeons of England.—5.15 p.m., Mr. John Foster: Diagnosis and Treatment of Orbital Tumours; 6.30 p.m., Mr. John Howkins: The Ureter in Pelvic Surgery.

Wednesday, October 6

Institute of Dermatology.—5.30 p.m., Dr. H. Haber: Normal Histology of the Skin.

Institute of Urology.—4.30 for 5 p.m., Mr. H. G. Hanley: Urological Problems in Pregnancy.

London University.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in pathology by Professor H. Fernández-Morán (Venezuela): Studies on Cell Ultrastructure with the Electron Microscope.

Midland Medical Society.—At Birmingham Medical Institute, 154, Great Charles Street, 8.15 p.m., annual general meeting. Valedictory address by Mr. R. P. Scott Mason: Medical Education, Past and Present.

●Royal College of Surgeons of England.—5.15 p.m. Mr. D. N. Matthews: Principles of Repair of Soft Tissue Injuries; 6.30 p.m., Mr. M. C. Oldfield: Hare Lip and Cleft Palate.

Thursday, October 7

London University.—At Clinical Lecture Theatre, Middlesex Hospital Medical School, 5.30 p.m., special university lecture in medicine by Dr. J. J. Wild (Minneapolis): Effect of Tissues on Pulsed Ultrasound including the Visualization of Cancer *in situ* in the Living Breast.

Nuffield Orthopaedic Centre, Wingfield-Morris Orthopaedic Hospital, Oxford.—8.30 p.m., Mr. J. G. Taylor and Dr. F. H. Kemp: Results and Complications of Lumbo-Sacral Fusion Operations.

Oxford University.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Mr. D. M. Wallace: Carcinoma of the Bladder.

●Royal College of Surgeons of England.—5.15 p.m., Professor Lambert Rogers: Non-traumatic Intracranial Haemorrhage; 6.30 p.m., Mr. V. H. Riddell: Simple Tumours of the Breast.

St. John's Hospital Dermatological Society, Lisle Street, London, W.C. —4.30 p.m., demonstration and discussion of clinical cases.

Friday, October 8

●Carmarthen Medical Society.—At Trinity College, Carmarthen, 8 p.m., lecture by Dr. L. G. C. E. Pugh (Everest Expedition).

●Institute of Dermatology.—5.30 p.m., Dr. O. L. S. Scott: Developmental Abnormalities—Clinical demonstration.

Institute of Diseases of the Chest.—5 p.m., Dr. N. C. Oswald: Clinical demonstration.

Institute of Laryngology and Otology.—3.30 p.m., clinical meeting for general practitioners. Mr. S. E. Birdsall: Chronic Ear Discharge.

London Association of the Medical Women's Federation.—At Royal Free Hospital School of Medicine, 8.30 p.m., Mrs. Mary Symes (Coroner for Eastern district of Suffolk): Coroner and the Doctor.

●Royal College of Surgeons of England.—5.15 p.m., Mr. H. E. Lockhart-Mummery: Fistula-in-Ano; 6.30 p.m., Professor C. F. W. Illingworth: Massive Gastro-intestinal Haemorrhage.

Saturday, October 9

International Haemophilia Society: South of Scotland Group.—At West Medical Theatre, Edinburgh Royal Infirmary, 3.30 p.m., open meeting.

Sunday, October 10

International Haemophilia Society.—At St. Pancras Town Hall, Euston Road, N.W., 2.30 p.m., general meeting. Address by Sir Lionel Whitby.

APPOINTMENTS

Charing Cross Hospital.—W. P. Greening, F.R.C.S., Part-time Assistant Surgeon (Consultant); D. A. B. Hopkin, M.D., F.F.A. R.C.S., D.A., D.T.M.&H., Part-time Consultant Anaesthetist.

Rivlin, S. M., M.R.C.S., L.R.C.P., Surgeon to Varicose Ulcer Clinic, Battersea Central Mission.

University College Hospital, Ibadan, Nigeria.—O. Wesley-James, M.B., B.S., Registrar (Department of Surgery); M. D. W. Low, M.B., Ch.B., M.R.C.P.Ed., D.Obst.R.C.O.G., Registrar (Department of Medicine); W. T. Fullerton, M.B., Ch.B., M.R.C.O.G., Registrar (Department of Obstetrics and Gynaecology); A. R. Isaac, L.R.C.P.&S.Ed., Senior House Officer (Department of Surgery); G. L. Money, M.B., B.S., Senior House Officer (Department of Medicine).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Brooks.—On September 19, 1954, at Panteg Hospital, Pontypool, Mon, to Mae, wife of Alexander Brooks, M.B., Ch.B., of Braeside, Beaufort, Mon, a son—Alexander Begg.

Swinscow.—On September 26, 1954, at Hitchin, Herts, to Josephine, wife of Dr. Douglas Swinscow, of Knebworth, Herts, a daughter.

Thorne.—On September 21, 1954, at the London Hospital, London, E., to Pamela (formerly Houchin), M.R.C.S., L.R.C.P., D.C.H., wife of Napier A. Thorne, M.D., M.R.C.P., of 21, Chester Road, Chigwell, Essex, a daughter.

Wright.—On September 9, 1954, to Isobel, wife of Dr. Gerald A. Wright, M.R.C.P., of 501, Medical Building, Lethbridge, Alberta, Canada, a daughter—Elizabeth Mary Jane.

DEATHS

Bowker.—On September 25, 1954, at his home, Newport, Mon, Richard Ryther Stancer Bowker, M.B., F.R.C.S.Ed., aged 58.

Fettes.—On September 24, 1954, at Weymouth, Dorset, David Fettes, C.B.E., M.B., F.R.C.S.Ed., Brigadier, late R.A.M.C., retired, aged 63.

Hetherington.—On September 25, 1954, in hospital, London, Vernon Hetherington, M.R.C.S., L.R.C.P., of 85, Bryanston Court, late of 31, Weymouth Street, London, W.1.

Hobbs.—On September 22, 1954, at Broughton, Hants, Geoffrey Charlstrom Hobbs, L.R.C.P.&S.Ed., L.R.F.P.S.

Janes.—On September 21, 1954, at the Middlesex Hospital, London, W., Leonard Robert Janes, M.B., B.Chir., of 6, Clarendon Terrace, Brighton, Sussex, aged 51.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Whooping-cough Immunization

Q.—*What degree of protection is given by whooping-cough vaccine, and for how long does it last? How worth while is immunization in view of the increased risk of paralytic poliomyelitis, the availability of gamma globulin for temporary protection, and the possibility of antibiotic therapy?*

A.—Experience with large-scale trials of whooping-cough vaccines, both here and in America, indicates that the attack rate in inoculated children varies from 1:3 to 1:10 of that in comparable uninoculated children, and that the attack in inoculated children who do develop the disease is usually shorter and milder than in the control group. Thus it may fairly be claimed that whooping-cough vaccines which have been shown by mouse tests or field trials to have good antigenic potency give a high degree of protection to young susceptible children. This protection lasts for at least two to three years. Whooping-cough is most severe in children under one year of age, and about two-thirds of the deaths from this infection occur in the first year of life. But whooping-cough in any child under 5 years can be a severe, protracted, and debilitating infection, so that prophylactic vaccination, if it is safe and effective, should certainly be offered to any pre-school child.

The hazard of post-inoculation poliomyelitis is, at the worst, a very small one, and seems to occur more with alum-containing prophylactics, and particularly perhaps with combined diphtheria toxoid and whooping-cough vaccine, than with straight toxoid or vaccine. The risk of this complication is probably less when injections are given to infants than with older children, and it can be prevented by avoiding inoculations at a time when poliomyelitis is prevalent in any particular area. There is little evidence of the value of gamma globulin in preventing whooping-cough, and of course it could be given only to known contacts in a family or nursery as soon as possible after the primary case was diagnosed. Unfortunately the primary case is not often diagnosed early, and this difficulty minimizes the possible value of both seroprophylaxis and chemoprophylaxis. It also reduces the efficiency of chemotherapy, since the results in controlled trials indicate that only cases of whooping-cough diagnosed in the first 7–10 days of infection are likely to benefit by a reduction in the number and severity of the paroxysms.

Abdominal Testes

Q.—*What advice regarding treatment should one give to a man of 30 with bilateral abdominal testes? What is the magnitude of the danger of malignancy arising?*

A.—If, as is probably the case, the testes are impalpable they are best left alone. Even if they could be placed in the scrotum, which is unlikely, spermatogenesis would not occur. If any complication suggesting torsion should occur, the offending testis should be removed. The patient should have a careful abdominal examination at intervals of about a year, and should be told to report any abnormal swelling at once. Malignant disease occurs in about 12% of cases of undescended testis, and its incidence is said to be about 50 times greater than it would be if failure of descent had no predisposing influence on its development. Few surgeons, however, would advise bilateral orchidectomy for abdominal testes as a prophylaxis against malignant disease in the absence of any symptoms.

Diagnosis of Non-paralytic Poliomyelitis

Q.—*What are the clinical features on which to base a diagnosis of non-paralytic poliomyelitis? Is it possible to make this diagnosis in the absence of paralytic cases, or of a history of contact with a paralytic case? Are there any laboratory tests which can confirm the diagnosis?*

A.—The clinical diagnosis of non-paralytic poliomyelitis can seldom be made with certainty, but the symptoms and signs are often highly suggestive of this diagnosis, for they are the same as occur before paralysis in the paralytic form of the disease. Perhaps the most important clinical features are the development of spinal pains with meningeal symptoms and signs, with some fever but usually without the patient being either seriously ill or mentally confused. The spinal pains may be severe or slight and may be referred to the back of the neck, the mid-dorsal, or the sacral region. Root pains or paraesthesiae in the thighs or trunk may also occur. When meningeal symptoms are severe lumbar puncture is imperative for the exclusion of conditions such as meningitis which require the earliest possible diagnosis and treatment. The changes in the cerebrospinal fluid are well known, but are not in themselves diagnostic of poliomyelitis.

As regards laboratory tests, they are of value only in retrospect, for the most reliable depends on the development of antibodies to the virus concerned. Isolation of the virus from the stools provides supporting evidence.

Transplantation of Teeth

Q.—*Thomas Rowlandson (1756–1827) painted some vivid pictures of teeth being transplanted from one person to another. Is this operation ever done now, and, if so, what are the results? What are the indications for it, and where do the donor teeth come from?*

A.—Transplantation of teeth from one person to another was practised many years ago but has long since been discontinued on ethical grounds. It is understood that such teeth after an initial period of splinting sometimes remained firm for periods of up to ten years, but were eventually lost as a result of resorption of the roots. The mechanism by which they were retained was largely mechanical, new bone being laid down within the areas of resorption.

Nowadays a tooth is sometimes replaced when completely dislocated as a result of an accident or in the course of manipulating a partially dislocated tooth. If this is done at once in a young patient the results are occasionally good. If, however, the tooth has been out for any length of time the pulp will certainly die. In these circumstances the pulp is sometimes removed, the root canal filled, and the tooth sterilized before replacement. Such teeth may be retained for a time, but are usually lost within a few years.

Blood Pressure and Pulse Rate

Q.—*Both high blood pressure and a rapid heart beat would seem to be devices for increasing blood supply, generally or locally. Can one have a persistently high blood pressure and a slow pulse? Is there any correlation between the rate of the heart beat and the blood pressure, and where is the literature on this point?*

A.—When a blood pressure raising agent is given which does not of itself excite the heart to beat more quickly, the pulse rate slows owing to a carotid sinus reflex, the sinus being stimulated by the raised pressure within it and the reflex causing an increase of vagal tone. When the heart rate is naturally slow, as in sinus bradycardia or complete heart block, an increased stroke volume results in a rise of systolic blood pressure, but the diastolic pressure remains normal or even rather low. Some of the adrenergic drugs, however, increase both the blood pressure and the pulse rate and this is well seen physiologically under conditions of excitement. When there is vasodilatation and pooling of blood in the periphery, a low blood pressure may be associated with tachycardia, as in shock, for example. In the vaso-vagal faint an initial fall of blood pressure is

associated with bradycardia; when the bradycardia is replaced by tachycardia, either naturally or as the result of atropine, the blood pressure does not necessarily rise and the patient may remain unconscious. These are just a few of the many examples of the varying relationship between blood pressure and pulse rate. The whole subject is fully described in any standard textbook of physiology.

Tuberculosis from Pets

Q.—*A child of 11 was given a kitten. For seven months the kitten ailed, coughing and sneezing, and was thought to have cat asthma. The kitten died. Post-mortem examination showed extensive pulmonary tuberculosis. What are the chances of the kitten infecting the child? Is it known how often tuberculosis is derived from pets, and, if not, what is your estimate?*

A.—Cats are said to be susceptible only to the bovine tubercle bacillus. This, of course, might be transmitted to the child in question, as the kitten had pulmonary tuberculosis. The child should therefore be treated as if he were a contact of a human case; a Mantoux test should be done, and, if positive, he should have his chest radiographed. If the Mantoux test is negative it should be repeated in six weeks. Rich[1] quotes figures suggesting that 1 to 5.6% of cats living in large cities are tuberculous. But these figures date from before 1923; with the decrease in dangerous milk in the last 20 years the figure must now be much lower. For dogs Rich quotes figures of 0.3–9.0%. Dogs are susceptible to the human bacillus and are liable to develop pulmonary tuberculosis, so that they must be regarded as potential sources of infection. With the large number of human sources in the community, pets have, possibly unjustifiably, been neglected. Perhaps we should start veterinary contact clinics. Beyond the above facts, we know no evidence on which to base an estimate of the frequency of infection from pets.

References

[1] *The Pathogenesis of Tuberculosis*, 1951, 2nd ed. Blackwell.

Alpha-naphthylamine and Cancer

Q.—*A chemist now aged 71 has a carcinoma of the bronchus. A few years ago he did three months' work on the purification of alpha-naphthylamine. Is there likely to be any connexion between this and his present condition?*

A.—It is most unlikely that the work in connexion with the purification of alpha-naphthylamine has had anything to do with the carcinoma of the bronchus. Alpha-naphthylamine is one of the group of intermediate dyestuffs suspected of causing cancer of the bladder, but the evidence is not as strong for alpha- as it is for beta-naphthylamine. Few cases of bladder cancer have been described in alpha-naphthylamine workers, and when they have arisen the chemical has been found to contain beta-naphthylamine as an impurity. Both chemicals gain access to the body mainly through the respiratory tract, and no cases of cancer of the lung have been recorded in the exposed workers.

Nerve Impulses and Tumour Growth

Q.—*Is there any evidence that interruption of the nerve supply of a limb protects it from the development of new growths?*

A.—There is no evidence that tumour growth is stimulated or inhibited by nervous impulses. It may be that if denervation of a limb produced arteriolar dilatation this would tend to favour cellular multiplication rather than the reverse.

Adrenaline Test

Q.—*What are the details of the adrenaline test for pituitary-adrenal function? How should it be interpreted and how reliable is it?*

A.—The adrenaline test for pituitary-adrenal function is quite unreliable, and should not be used for this purpose.

NOTES AND COMMENTS

Reliability of Mass Miniature Radiography.—Professor R. C. Browne and Mr. D. J. Newell (Newcastle-upon-Tyne) write: Although the findings of Birkelo *et al.*[1] ("Any Questions?" September 18, p. 711) show that there is little to choose between miniature and full-size film for the detection of tuberculous pulmonary abnormalities, the same may not be true for all pulmonary abnormality. In a recent investigation into the radiological diagnosis of coal-miners' pneumoconiosis (Newell and McCallum[2]), full-size (15 by 12 in.—38 by 30 cm.), 4 by 5 in. (10 by 12.7 cm.), and 70-mm. chest radiographs were compared. Each of 139 miners was radiographed by the three techniques, and each of three experienced viewers independently classified the films three times as Category 0 (Normal), 1, 2, 3, or Complicated. As in the American work, there were considerable differences between observers reading the same set of films, and between the readings of one film made by the same observer on different occasions. The main finding of the investigation, however, was that the 4 by 5 in. films gave results on the average one whole category lower than the large films, while the 70-mm. film readings were 0.6 of a category lower. This unfavourable result for small films is not surprising when the size of the lesions in simple pneumoconiosis is considered. Scattered opacities which are just large enough to be seen in the large film might easily become invisible in the 70-mm. or the 35-mm. film. Although miniature techniques appear to be as effective as the large film in detecting the larger lesions found in tuberculosis, it may be unwise to assume that this is true for all radiological abnormality of the chest.

Our Expert writes: My answer was in reply to a question which asked about the effectiveness of radiography in detecting pulmonary neoplasm and pulmonary tuberculosis (not chest diseases in general), and the relative efficiency of miniature and full-size radiography for these purposes. In fact, most of the work in this field has been done in relation to the detection of tuberculosis, but it was a reasonable assumption that the results could be applied also to the detection of pulmonary neoplasm. I entirely agree with Professor Browne and Mr. Newell that the assumption cannot be carried outside those fields, and indeed that in the specific example of coal-miners' pneumoconiosis it would not be justified. The results they quote, however, refer to an assessment of degree of pneumoconiosis, not the detection of abnormality—though I suspect that some cases of pneumoconiosis would be missed by miniature methods. The point is that miniature radiography, as a result of dual reading, has been adequately established as a satisfactory method of tuberculosis case-finding, but further work is still required before it is accepted as satisfactory for case-assessment or detection of other conditions; it may further be accepted that on the evidence at present available miniature methods are not suitable for the detection of pneumoconiosis.

References

[1] *J. Amer. med. Ass.*, 1947, **133**, 359.
[2] *J. Fac. Radiol.*, 1954, **6**, 67.

Itching in Hodgkin's Disease.—Dr. F. Arnot Bearn (Buxton) writes: On three occasions I have found that the itching in leukaemia ("Any Questions?" September 11, p. 657) was relieved by daily injections of adrenaline. Why, I do not know.

Correction.—We regret that in Dr. G. L. Jones's letter on pancreatic carcinoma (*Journal*, September 25, p. 753) Professor Allen O. Whipple's name was wrongly spelt.

Refresher Course Books.—The first two volumes of collected articles from the Refresher Course for General Practitioners published in the *Journal* are now available. The first volume contains 55 articles and the second 60. Each article has been revised by its author. Copies of both volumes may be obtained, price 25s. (postage 1s.) each, direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers. The second book of **"Any Questions?"** is also available, price 7s. 6d. (postage 6d.).

All communications with regard to editorial business should be addressed to The Editor, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: Euston 4499. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: Euston 4499. Telegrams: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. Telephone: Euston 4499. Telegrams: *Medisecra, Westcent, London.*

B.M.A. Scottish Office: 7, Drumsheugh Gardens, Edinburgh.